CHAPTER 19

IMMUNOLOGIC EVALUATION

INTRODUCTION

Background

Overt damage to organs of the immune system and depressed immunologic function have been noted in a variety of animals exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). As the fields of immunology and immunotoxicology have grown within the past 10 years, a significant spectrum of subtle immunotoxic effects has also been described in animals, but for many possible reasons, comparable adverse effects have not been consistently recorded in exposed human individuals or cohorts.

Thus, an intensive search is under way to ascertain the effects of TCDD on the human immune system, particularly with respect to the development of cancer. Most ongoing dioxin morbidity studies in the United States have incorporated comprehensive laboratory assessments of the immune system.

Numerous animal studies have demonstrated significant immunotoxicity following the administration of TCDD. The relatively consistent observations of decreased thymus weight (with cortical atrophy and a depletion of lymphocytes), atrophy of other lymphoid tissue, depressed cellular bone marrow, and decreased humoral and cell-mediated immunity and increased susceptibility to infection have been noted in a variety of animals, including monkeys, rabbits, guinea pigs, rats, and mice.[1-13] The immune-response effects varied by species, species strain, age, integrity of the endocrine system, dose, and route of administration. Generally, the immunologic parameters returned to normal or approximate normal values over time, even following moderate to high doses of TCDD.

2,4-D and numerous congeners of TCDD have been studied to determine if similar immune system effects occur. 2,4-D has been studied extensively in mice, using numerous uptake methods, and the only immune effects found are probably acute secondary effects seen at very high doses.[14-16] Several congener studies have found varied results with 2,7-dichlorodibenzo-p-dioxin and 1,2,3,4,6,7,8-heptachlorodibenzo-p-dioxin, producing similar results to TCDD, while octachlorodibenzo-p-dioxin had no effect on the immune system.[17-19]

The immune system is so sensitive to TCDD that immune function in animals has frequently been used as a marker of acute toxicity in the absence of other biologic effects.[20] The mechanism of TCDD immunotoxicity is under intensive investigation by molecular biologists, pathologists, and geneticists. In general, TCDD toxicity is probably linked to the Ah receptor, and specifically to the Ah^b allele, which governs microsomal enzyme induction as reflected by aryl hydrocarbon hydroxylase and cytochrome P-448/450 levels.[21-26] This premise underscores the questions of the degree to which the human response to TCDD is dependent upon the Ah locus or other genetic receptors, and how this response is manifested in the immune system. Investigations into the

mechanisms of action, primarily involving the B cell (and, to a lesser extent, the T cell), have produced consistent results. The effects of TCDD appear to depend on the age of the cells they affect, with the youngest cells affected the most. Thus, a number of researchers have hypothesized that TCDD interferes with an early event in cell maturation.[25,27-36]

Animal studies and several observational studies in humans have shown variable results. Data from the Times Beach, Missouri, episode disclosed no group differences for various T-lymphocyte populations, proliferative responses to phytohemagglutinin (PHA), concanavalin A, pokeweed or tetanus toxoid stimulation, and in skin testing with seven antigens.[37] A report of the assessment of the immune system of men exposed to TCDD in an industrial accident in Britain did not discuss the results of the measurement of the immunoglobulin profile, lymphocytes, T and B cells, response to PHA, and three hematologic variables.[38] A prior publication on the same cohort cited unpublished findings of Ward, suggesting a reduction in the capacity of the "primary" immune system.[39]

A longitudinal evaluation of 48 highly exposed children (one-half with chloracne) from the July 1976 Seveso incident showed significantly elevated complement hemolytic activity over six measurements during the period 1976 to 1979 (although the biologic significance of this is unknown) and an increased proliferative response to PHA and pokeweed during the first three screenings.[40] This study was characterized by a shifting study population over the observation period and by excessive laboratory variation that may have masked other true group differences. Nonetheless, the Seveso data may be interpreted as indicative of a stimulated immune system, particularly cell-mediated immunity, differing substantially from the bulk of animal studies, which showed decreased activity.

A followup study conducted 17 years after an accident compared 18 workers exposed to dioxin to a carefully selected control group. No significant differences were found between workers and controls for T-lymphocyte, B-lymphocyte, CD4 cell (helper T-cell), and CD8 cell (suppressor T-cell) counts in peripheral blood. However, there was a significantly higher number of natural killer cells, as identified by monoclonal antibody Leu-7.[41]

A recent study of residents of the TCDD-contaminated Quail Run Mobile Home Park in Missouri also revealed data that conflicted with the Seveso experience.[42] A statistically significant amount of anergy and relative anergy was detected in the TCDD-exposed group, as determined by the multitest applicator (seven-antigen test system). Interreader variation and skin test antigen quality presented major interpretive difficulties. Nevertheless, findings suggestive of decreased cell-mediated immunity were provided by decreased CD3 (T_3), CD4 (T_4), and CD2 (T_{11}) cell percentages. Also noted was an increased lymphoproliferative response to pokeweed mitogen (PWM). The overall depression of immunologic response was not correlated with an increase in clinical disease. A later (1988) followup of those participants with initial anergy found no anergy.[43]

Baseline Summary Results

Immunologic function and phenotypic marker studies were performed on 592 participants (297 Ranch Hands, 295 Comparisons) randomly selected by the

terminal digit of their case number. Because of laboratory problems (e.g., fluctuating quality control and lack of simultaneous differential counts on the peripheral mononuclear cells), a review committee was convened at Baseline to determine which data were relevant for analysis. Such decisions were made on a case-by-case basis without knowledge of Ranch Hand or Comparison group membership. The committee concluded that the data could be analyzed on a group basis, but interpretation of data on an individual basis was inappropriate.

Analyses of the cell surface markers (CD2 or T_{11}, CD3 or T_3, CD4 or T_4, CD8 or T_8, CD20 or B, the CD4/CD8 or T_4/T_8 ratio, and the total lymphocyte count [TLC]) showed no significant group differences. However, increased smoking was significantly associated with increases in most cell counts but not with the CD4/CD8 ratio and CD20 cells, whereas increasing age was significantly associated with decreasing TLC and CD8 cells.

Functional studies of T and B cells via reaction to antigenic (tetanus toxoid) or mitogen (PHA, concanavalin A, and pokeweed) stimulation showed no group differences. Similarly, unadjusted and adjusted mean values of the four assays were not significantly different between groups, but one unstimulated control value (reflecting Baseline thymidine uptake by T cells) was significantly decreased in the Ranch Hands. The biologic relevance of this finding was unclear.

Further, in the covariate analysis of the functional studies, group-by-smoking and group-by-alcohol interactions were noted. Of greater importance, however, was the finding that lymphocytic response increased with smoking, but decreased with age.

In summary, neither immunologic function nor cell marker studies showed significant impairment in the Ranch Hand group, or patterns supportive of a herbicide effect. Smoking was associated with a significant increase in the marker cells CD2, CD3, CD4, and CD8, and in the TLC, with a concomitant increase in lymphocytic response to PWM.

1985 Followup Study Summary Results

The 1985 Air Force Health Study (AFHS) physical examination placed more emphasis on the immunologic assessment than did the 1982 Baseline profile. Immunologic competence was measured by cell surface marker (phenotypic) studies and cell stimulation studies on 47 percent of the study population, and by a series of four skin test antigens in 76 percent of the participants to assess the delayed hypersensitivity response.

Surface marker studies were conducted for CD2 cells, CD4 cells, CD8 cells, CD20 or B cells, CD14 cells or monocytes, and HLA-DR cells; the ratio of CD4/CD8 cells was included in the analysis. Because of inherent significant day-to-day and batch-to-batch variation, all results (including functional stimulation studies) were adjusted for blood-draw day variation. Statistical testing of the seven phenotypic cell markers did not reveal any significant group differences (interactions excepted), either unadjusted or adjusted, for the covariates of age, race, occupation, current smoking, lifetime smoking history (in pack-years), current alcohol use, or lifetime

alcohol use (in drink-years). Similarly, none of the unadjusted or adjusted analyses of the functional stimulation studies (for PHA, PWM, or mixed lymphocyte culture [MLC]) showed any statistically significant group differences. However, the adjusted analyses for CD2, CD20, CD14, HLA-DR cells, PWM, and net MLC stimulation showed some significant group-by-covariate interactions, precluding direct adjusted group contrasts. Overall, no discernible pattern was identified to suggest a detriment in any subgroup of either the Ranch Hands or Comparisons.

The covariate effects of age, race, smoking, and alcohol use affected most variables in the phenotypic and stimulation studies. Consistently decreasing values of all cell markers and stimulated cells were associated with increasing age, whereas increased levels of smoking were usually associated with increases in the values of those variables. Blacks had consistently higher stimulated cell counts than nonblacks, but this effect was not observed for counts of T cells, B cells, or HLA-DR cells. Enlisted personnel generally had higher cell surface marker counts than officers.

Exposure index analyses of cell surface markers revealed no pattern consistent with a dose-response relationship. For enlisted groundcrew, the mean CD2 and CD8 cell counts for the medium exposure group were significantly lower than those with low exposure, but were slightly lower than those with high exposure. The exposure index analyses of the functional stimulation tests revealed no consistent significant dose-response patterns for net PHA counts or net MLC counts. For net PWM counts, enlisted flyers in the high exposure level had a significantly lower adjusted count than enlisted flyers in the low exposure level, and a decreasing trend was apparent.

The delayed hypersensitivity response was assessed by the skin test antigens of mumps, Candida albicans, Trichophyton, and staphage-lysate. The 48-hour measurements of skin induration and erythema for the four tests showed marked interreader variation and analyses showed that one of the three skin test readers measured induration larger than erythema (a clinically unacceptable finding) in an average of 30 percent of the readings. Consequently, all skin test data were declared invalid and were not used in the assessment of group differences. The skin test reading problems led to the use of additional clinical quality control procedures for the 1987 AFHS followup examination.

In conclusion, no significant group differences were found for the comprehensive cell surface marker or functional stimulation studies. The effects of age, smoking, and alcohol use were observed in these immunologic tests. The assessment of delayed hypersensitivity skin responses was precluded by poor data quality and excluded from further analysis. Overall, there was no consistent indication of impaired immunologic competence in either group.

Rationale of the Immunologic Measurements

Because of rapid changes in the knowledge of the immune system, Table 19-1 is provided as an aid in interpreting the medical significance of the immunologic data. The table provides rationales and endpoints for various immunologic measurements analyzed as part of antigen skin tests, cell surface

TABLE 19-1.

Medical Significance of the Immunologic Data

Immunologic Measure	Rationale of the Measurement	Disease/Syndrome/Condition Endpoint
Skin Tests		
Candida Mumps Tricophyton Staphage-lysate	Each measures skin reactivity induced by specific antigen injected intradermally and correlates with recall T cell sensitivity to the antigen.	Antigen reactivity or sensitivity; anergy.
Marker Studies		
CD2 (T11)	Measures CD2 cells coincident with sheep rosette receptor on cell surface (most are CD4 and CD8 cells).	Decreased in immune deficiency; increased with lymphoproliferative disorders.
CD20 (B1)	Measures peripheral blood B cells; no reaction with T cells, granulocytes, or monocytes.	Decreased in immunodeficiency; increased in lymphoproliferative disorders.
CD4 (Leu3a+b)	Measures T cells that exhibit helper/ inducer phenotype.	Decreased in AIDS; increased in autoimmune diseases.
CD8 (OKT8)	Measures T cells that exhibit suppressor/ cytotoxic functions.	Variable in autoimmune diseases; increased in some viral illnesses and immunodeficiencies.
CD14 (LeuM3)	Measures mature monocytes in peripheral blood.	Increases with inflammation.
CD25 (IL-2 Receptor)	Present on activated T cells; absent on normal peripheral blood lymphocytes, monocytes, and granulocytes.	Increased in lymphoproliferative disorders.

TABLE 19-1. (continued)

Medical Significance of the Immunologic Data

Immunologic Measure	Rationale of the Measurement	Disease/Syndrome/Condition Endpoint
HLA-DR	Measures cells expressing HLA-DR antigen; includes B cells and monocytes.	Decreased in B cell deficiency; decreased in agammaglobulinemia.
CD4/CD8 Ratio	Measures proportional difference between CD4+ cell populations and CD8+ cell populations.	Decreased in immunodeficiencies and viral illnesses.
TLC	Measures absolute number of total lymphocytes circulating in peripheral blood.	Decreased in immunodeficiency; increased in lymphoproliferative disorders.
Immunoglobulins		
IgG IgA IgM	Each measures ability of specific B-cell subgroup to secrete specific antibody class of molecules.	Increased in hyperglobulinemia or myeloma. Decreased in selective or total B cell immunodeficiency.
Functional Studies		
PHA	Measures functional capability of T cells to become activated by mitogen and undergo proliferation.	Decreased with impaired natural defenses.

TABLE 19-1. (continued)

Medical Significance of the Immunologic Data

Immunologic Measure	Rationale of the Measurement	Disease/Syndrome/Condition Endpoint
NKCI (with IL-2) NKCA (without IL-2)	Measures natural killer cell lytic activity with and without Interleukin 2 (IL-2) treatment of the natural killer cells. Percent release relates the amount of chromium-51 released when target cells are killed by natural killer cells to the amount of chromium-51 released when all target cells are killed (maximal release of radioactivity). Net response cpm is generated by the release of isotope from target cells killed by natural killer cells minus the cpm generated by spontaneous lysis or isotope leakage of the target cells.	Decreased with impaired natural defenses.
MLC	Measures reactivity of T cells to foreign histocompatibility antigens on unrelated lymphocytes.	Increased HLA sensitization and transplantation.

marker studies, TLC, quantitative immunoglobulins, and functional stimulation studies. Normal ranges are not provided for many of these variables because there is no consensus among immunologists as to what the normal ranges are for these measures of immune function. The absence of normal ranges makes interpretation of the results difficult.

Several new immunologic parameters were added to the 1987 study. Since slight impairments in response have been noted in patients with Hodgkin's Disease, lower concentrations and a shorter culture time were added to the PHA assay. The concentrations and incubations were used to detect very subtle changes in immune response that might be overwhelmed by larger doses and longer incubation times. The levels of natural killer cell activity are modulated by Interleukin 2. Therefore, natural killer activity (both net release and percent release) was measured in the presence and absence of Interleukin 2. Humoral immunity was assessed by the determination of quantitative immunoglobulins.

Skin Testing for Delayed Cutaneous Hypersensitivity (DCH)

The screening test for T-cell mediated immunodeficiency was performed using the same four skin test antigens and doses as in the 1985 followup examinations. The antigen doses were lower than those recommended by the World Health Organization (WHO) Scientific Group on Primary Immunodeficiency Diseases[44] but did not produce significant morbidity impairment of function for participants in the 1985 examinations. The following antigen doses were used:

1) Candida albicans, Hollister-Stier, Spokane, Washington, Lot #G96H614001, 1:1000 weight/volume, 0.1 ml intradermal.

2) Mumps skin test antigen, USP MSTA (TM), Connaught Laboratories, Inc., Swiftwater, Pennsylvania, Lot #6081028, 2 complement-fixing units, 0.05 ml, intradermal (each ml contains 40 complement-fixing units).

3) Trichophyton mix (T. tonsurans, rubrum and mentagrophytes), Hollister-Stier, Spokane, Washington, Lot #K97B142401, 1:1000 weight/volume, 0.1 ml intradermal.

4) Bacterial antigen made from staphylococcus, STAPHAGE LYSATE (SPL)®, Delmont Laboratories, Inc., Swarthmore, Pennsylvania, Lot #6120694, 6-9 X 10^6 colony-forming units of S. aureus and 0.5-5 X 10^7 staphylococcus bacteriophage plaque-forming units (PFU) 0.05 ml, intradermal (each ml contains 120-180 million colony-forming units of S. aureus and 100-1000 million bactiophage PFU).

Responses to the skin test were noted at 48 hours. Two experienced vocational or registered nurses from the Scripps Clinic and Research Foundation (SCRF) Division of Allergy and Immunology, independently measured the size of both induration and erythema by the "pen method" using millimeter ruler. They recorded the greatest length and perpendicular breadth measurements for each of the four test sites per participant. In addition, for quality control purposes, each nurse reread 10 percent of the participants based on the

terminal digit of the participant identification number. A staff physician from the SCRF Division of Allergy and Immunology reviewed readings when induration was less than 5 mm for all four tests and rendered decisive judgment regarding the "correct" reading.

A "positive skin test" was defined by the 1986 WHO criteria as induration equal to or greater than 5 mm by any reading(s) judged to be valid (concordance between the nurse readings or verified by a physician); the presence of one or more positive skin tests in an individual participant was interpreted as "normal" DCH, indicative of intact cell-mediated immunity. When all four tests were negative by all valid readings, the interpretation was "possibly abnormal," that is, unresponsive to the antigen doses applied. Because antigen doses recommended by WHO were not used, a definitive interpretation of "defective cell-mediated immunity" was not rendered.

Immunology Methodologies

The isolation of mononuclear cells from peripheral blood was the first step for testing immune competence and enumeration of phenotypic markers. Whole blood collected in Acid Citrate Dextrose-Solution A (ACD-A) was obtained from each patient. Peripheral blood mononuclear (PBM) cells were isolated by Ficoll-Hypaque density gradient centrifugation. The PBM cells were then washed and resuspended in HB101 media (HANA Biologics, Inc.) supplemented with 10M (million) units/ml penicillin, 10,000 mcg/ml streptomycin, 1 percent sodium pyruvate (100 mM [millimolar]), and 1 percent L-glutamine (200 mM). To determine percent monocyte and granulocyte contamination of the PBM cell preparations, an aliquot of the cells was stained with a nonspecific esterase stain. PBM cell concentration was adjusted for each individual assay.

Cell Surface Marker Analysis

Mouse monoclonal antibodies directed against specific surface markers were used to identify and quantitate different cell populations in the peripheral blood of the participants. Mononuclear cell concentrations adjusted to 1.0×10^6 cells/ml in RPMI media and 10 percent fetal calf serum (FCS) were incubated with the following fluorescein isothiocyanate conjugated monoclonal antibodies: CD8(OKT8*), CD4(Leu3a+b**), CD14(LeuM3**), CD25(IL-2 Receptor**), HLA-DR(HLADR**), CD2(T11***), and CD20 B1***). These cell surface antibodies measure total numbers of T and B lymphocytes, monocytes, helper T lymphocytes, suppressor T lymphocytes, activated T cells, and those cells carrying the HLA-DR antigen. A flow cytometer (Spectrum III, Ortho Diagnostic Systems, Raritan, NJ) was used to measure the percent of cells positive for each surface marker and absolute numbers were calculated.

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*Ortho Diagnostic Systems, Raritan, NJ.
**Becton Dickinson Immunocytometry Systems, Inc., Mountain View, CA.
***Coulter Immunology, Hialeah, FL.

TLC

TLC measures the absolute number of total lymphocytes circulating in the peripheral blood. Complete blood counts and differential white cell counts were obtained on peripheral blood specimens obtained from participants the same day they were drawn for the immunologic tests. All complete blood counts were performed using an electronic particle counter (Coulter S Plus®, Coulter Corporation, Hialeah, FL). Trilevel controls were run with each batch of samples. Two hundred cell manual differential counts were performed to obtain the percentages of different white blood cells present in each patient sample. Absolute lymphocyte counts were calculated by multiplying the white blood cell count by the percent lymphocytes counted in the differential. Results are reported as cells/mm^3.

Quantitative Immunoglobulins

Quantitative levels of IgG, IgA, and IgM were measured by rate nephelometry. The instrument automatically diluted and delivered the patient sample to the reaction flow cell along with the appropriate antibodies (antihuman IgG, IgA, and IgM, Beckman Instruments, Inc., Brea, CA) and other reaction constituents. Out-of-range and antigen excess checks were automatically performed before the nephelometer derived the final result in concentration units for the analytes in question. Tri-level controls were run with each batch of samples. Instrument calibration was accomplished by running a single protein concentration in duplicate and comparing it to the calibrator serum target value. The calibration factor derived was used to adjust the analyzer gain so that the raw calibration values equal the target values.

PHA Mitogen Stimulation Assays

Mitogens were used to stimulate the proliferation of lymphocytes in vitro. During the proliferative response, the lymphocytes undergo blast transformation and incorporate radioactive thymidine into their deoxyribonucleic acid. Participant lymphocyte concentrations were adjusted to 2.0×10^6 cells/ml in supplemented HB101 media. Samples were cultured in quadruplicate. Individual cultures consisted of 0.1 ml of cell suspension and 0.1 ml of mitogen solution in microtiter plates. The cultures were incubated in an atmosphere of 5 percent CO_2 at 37 degrees Celsius. Participant cells were cultured with three concentrations of PHA (18, 6, and 2 µg/ml, Sigma Chemical Co., St. Louis, MO) for 3 and 4 days. The cultures were pulsed with tritiated thymidine (1.0 µCi/microtiter well) for 4 hours and then harvested on a multiple automated cell harvester. Cellular proliferation was assessed by determining the tritiated thymidine uptake measured by taking the mean value of quadruplicate assays obtained through liquid scintillation counting.

Mixed Lymphocyte Reaction

Histocompatibility antigens can stimulate lymphocytes causing blast transformation. Donor lymphocytes were used to stimulate the proliferation of lymphocytes in vitro. A pool of freshly isolated lymphocytes was prepared

daily from controls and study participants to ensure a random mix of HLA antigens. The pooled stimulator cells were inactivated by irradiation (3,000 rad). Stimulator pools and participant lymphocyte concentrations were adjusted to 1.0 x 10^6 cells/ml in supplemented HB101 media. Samples were cultured in quadruplicate. Individual cultures consisted of 0.1 ml of responder cell suspension and 0.1 ml of stimulator cell suspension, in microtiter plates. The cultures were incubated in an atmosphere of 5 percent CO_2 at 37 degrees Celsius for 6 days. The cultures were pulsed with tritiated thymidine (1.0 µCi/microtiter well) for 16 hours and then harvested on a multiple automated cell harvester. Cellular proliferation was assessed by measuring tritiated thymidine uptake.

Natural Killer Cell Assays

Mononuclear cells from the participants were evaluated to assess the ability of certain peripheral blood cells to kill cells from a K-562 leukemia cell line. The K-562 cells (target cells) were preincubated with radioactive chromium (^{51}Cr) at 37 degrees Celsius in 5 percent CO_2 for 1 hour, washed, and the cell concentration adjusted to 1.6 x 10^6 cells/ml. Participant lymphocytes (effector cells) were adjusted to a concentration of 1.0 x 10^6 cells/ml; 2.7 ml of this concentration was incubated with 2.7 ml of 100 units/ml of recombinant Interleukin 2 (Amgen Biologicals, Thousand Oaks, CA) for 18 hours at 37 degrees Celsius. This preparation was then centrifuged and resuspended in 1 ml of media for a final concentration of 2.7 x 10^6 cells/ml. Participant lymphocytes not incubated with Interleukin 2 were also adjusted to a concentration of 2.7 x 10^6 cells/ml in RPMI media and 10 percent FCS. Fifty µl of the radioactive target K-562 cells were dispensed to each well of a microtiter plate. Quadruplicate 150 µl aliquots of participant lymphocytes (with and without Interleukin 2 preincubation) were dispensed to the microtiter plate. The final effector:target ratio was 50/1. Four wells contained media alone to determine the spontaneous release of radioactivity from the K-562 cells. Four wells contained 1 percent Triton X-100 to determine maximal release of radioactivity. The microtiter plates were centrifuged briefly at low speed and incubated at 37 degrees Celsius in 5 percent CO_2 for 3 hours. A 100 µl aliquot of the supernatant was removed from each well and counted on a gamma counter. Percent chromium release from the K-562 cells was determined.

Parameters of the 1987 Immunologic Evaluation

Dependent Variables

Data from the physical examination and the Scripps Immunology Reference Laboratory (SIRL) were used in the immunologic evaluation. Immunologic tests were carried out on a random sample of approximately 40 percent of the participants because of the complexity of the assay and the expense of these tests. Blood was drawn for testing from approximately one-half of these randomly chosen participants on the first day of the physical examination, and blood was drawn from the rest of the selected participants on the second day.

All participants except those chosen to receive the immunologic tests at SIRL on day 2 of the physical examination were scheduled to receive the skin

test as a part of the physical examination (approximately 80 percent of the 1987 followup participants). Participants chosen to receive the immunologic blood draw on day 2 of the physical examination were not given skin tests to avoid any effect the skin tests might have on the cell counts and functions.

Physical Examination Data

Physical examination data concerning the skin tests were used to evaluate immunologic function. A composite skin test diagnosis variable was constructed based on the reactivity to four separate antigens injected interdermally to measure antigen reactivity or sensitivity. This composite skin test diagnosis variable was analyzed as a discrete, dichotomous variable: each participant was considered possibly abnormal or normal based on his skin reactivity to the antigens Candida albicans, mumps, Trichophyton, and staphage-lysate. The response to each antigen was scored positive (normal) if the maximum diameter of the resulting 48-hour induration was greater than or equal to 5 mm, which indicated intact cell-mediated immunity. If none of the four antigen responses was positive, the composite skin test diagnosis was scored possibly abnormal. If one or more of the four antigen responses was positive, the composite skin test was considered normal.

Participants taking anti-inflammatory (except aspirin) or immunosuppressant medication, or who had recently received x-ray treatment or chemotherapy for cancer (as reported in the 1987 health interview questionnaire and verified by medical records review) were excluded from all analyses of skin test data. In addition, data from participants in examination group 2, except for one participant, were not used in the analysis of the composite skin test diagnosis variable, since they received staphage-lysate at a different dosage than all the other examination groups. One of the two nurses made a dosage error affecting all but the one participant in examination group 2.

Laboratory Examination Data

From the SIRL immunologic tests, the results of cell surface marker studies, TLC, quantitative immunoglobulins, and functional stimulation studies were analyzed. These data were evaluated to determine whether the natural logarithm scale was more appropriate for use with the statistical procedure(s) than the original scale. Table P-1 of Appendix P summarizes the statistics used in the assessment. The descriptive statistics of skewness and kurtosis were used in conjunction with the Kolmogorov D statistic for deciding whether to use the original scale or the natural logarithm scale.[15]

Participants taking anti-inflammatory (except aspirin) or immunosuppressant medication, or who had recently received x-ray treatment or chemotherapy for cancer were excluded from all analyses of laboratory data.

Quantitative Studies: Cell Surface Marker (Phenotypic) Studies

Quantification of the different cell populations was carried out with the use of mouse monoclonal antibodies. Seven cell surface markers and a ratio of

cell markers were analyzed in the evaluation of the immunologic system. The units of measurement (for all variables except the CD4/CD8 ratio) was cells/mm^3. These variables were treated as continuous data, and were subjected to the natural logarithm transformation for statistical analysis.

Quantitative Studies: TLC

Statistical analysis on TLC was performed. The units of measurement are cells/mm^3. A natural logarithm transformation was applied to the TLC data for statistical analyses.

Quantitative Studies: Immunoglobulins

The immunoglobulins IgG, IgA, and IgM were also analyzed statistically. The units of measurement are mg/dl. IgA and IgM were transformed by the natural logarithm for analyses.

Functional Stimulation Tests

Cell function responses to stimulation by PHA, MLC, and natural killer cell assays were also analyzed in the immunologic evaluation.

The following nine variables deriving from PHA stimulation were analyzed: unstimulated PHA response, the PHA net responses for three different concentrations and 2 harvesting days, an overall PHA net response (adjusting for concentration and day effects), and the maximum PHA net response among the three concentration levels and 2 harvesting days. Each observation was the result of the averaging of quadruplicate readings.

MLC of donor lymphocytes was also used to stimulate in vitro cell proliferation of participant lymphocytes; the following two variables deriving from MLC stimulation were analyzed: unstimulated MLC response and MLC net response.

The following four variables from the Natural Killer Cell Assays were analyzed:

- Natural Killer Cell Assay (NKCA):

  (1) NKCA 50/1 net response
  (2) NKCA 50/1 percent release

- Natural Killer Cell Assay with Interleukin 2 (NKCI):

  (3) NKCI 50/1 net response
  (4) NKCI 50/1 percent release.

The units of measurement for the PHA and MLC responses and the natural killer cell assays were counts per minute (cpm). These variables were treated as continuous in the statistical analysis. A natural logarithm transformation

was applied to the unstimulated PHA response and the unstimulated MLC response.

Covariates

Covariates examined in the immunologic evaluation, both in pairwise associations with the dependent variables and in adjusted statistical analyses, included the matching variables of age, race, and occupation; current alcohol use (drinks/day); lifetime alcohol history (drink-years); current cigarette smoking (cigarettes/day); and lifetime cigarette smoking history (pack-years). Further, batch-to-batch (examination group) variation and blood draw day-to-day variation (for each examination group) were also used as covariates for laboratory-dependent variables. Study participants who began their physical examination on the same day formed a batch. For the unstimulated PHA response, day of mitogen harvest was also used as a covariate in the adjusted analysis. For the overall PHA net response, mitogen concentration and day were used as covariates in the adjusted analyses.

In the discussion of the smoking covariates, the following terms are occasionally used: nonsmokers (those who never smoked cigarettes), former smokers (those who used to smoke cigarettes but currently do not), moderate smokers (those who smoke, on the average, more than 0 but not more than 20 cigarettes per day), and heavy smokers (those who smoke, on the average, more than 20 cigarettes per day). The categories of lifetime cigarette smoking history are 0 pack-years or nonsmokers; greater than 0 but not more than 10 pack-years, which will be referred to as moderate smokers; and greater than 10 pack-years or heavy smokers.

In discussing the alcohol-related covariates, the terms light, moderate, and heavy are occasionally used to describe the current drinking habits of the participants; for lifetime alcohol use, never replaces light. These distinctions correspond to the three drinking categories in Table 19-2 for current alcohol use and lifetime drinking history.

Relation to Baseline and 1985 Followup Studies

Of the variables analyzed in the 1987 immunologic assessment, all except CD25 cell marker, unstimulated MLC, TLC, maximum PHA net response, immunoglobulins, natural killer cell assays, and composite skin test diagnosis were analyzed in the 1985 assessment. For the 1985 assessment, the functional stimulation tests also included pokeweed net responses. This test was not performed in the 1987 evaluation. A portion of the variables of the 1987 assessment was also analyzed in the Baseline study.

Longitudinal analyses were performed on the CD4/CD8 ratio using the data collected for the 1985 followup and 1987 followup.

Statistical Methods

Most of the basic statistical methods used in the immunologic evaluation are described in Chapter 7. Due to the expected large variation from batch

TABLE 19-2.

Statistical Analysis for the Immunologic Evaluation

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Composite Skin Test Diagnosis (based on length of 4 skin test antigen induration measurements)	PE	D	Possibly Abnormal: 0/4 >5 mm Normal: ≥1/4 ≥5 mm	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC	UC:FT AC:LR CA:CS,FT UE:CS,FT AE:LR
CD2 Cells ($cells/mm^3$)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
CD4 Cells ($cells/mm^3$)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
CD8 Cells ($cells/mm^3$)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
CD20 Cells ($cells/mm^3$)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
CD14 Cells ($cells/mm^3$)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
CD25 Cells ($cells/mm^3$)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM

TABLE 19-2. (continued)

Statistical Analysis for the Immunologic Evaluation

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
HLA-DR Cells (cells/mm^3)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
CD4/CD8 Ratio	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM L:RM
TLC (cells/mm^3)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
IgG (mg/dl)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
IgA (mg/dl)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
IgM (mg/dl)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
Unstimulated PHA Response (cpm)	LAB	C	--	AGE,RACE, CC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH), DAY	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM

TABLE 19-2. (continued)

Statistical Analysis for the Immunologic Evaluation

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
PHA Net Response (day 1, concentration 1) (cpm)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
PHA Net Response (day 1, concentration 2) (cpm)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
PHA Net Response (day 1, concentration 3) (cpm)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
PHA Net Response (day 2, concentration 1) (cpm)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
PHA Net Response (day 2, concentration 2) (cpm)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
PHA Net Response (day 2, concentration 3) (cpm)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM

TABLE 19-2. (continued)

Statistical Analysis for the Immunologic Evaluation

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Overall PHA Net Response (cpm)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH), CONC,DAY	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
Maximum PHA Net Response (cpm)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
Unstimulated MLC Response (cpm)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
MLC Net Response (cpm)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
NKCA 50/1 Net Response (cpm)	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
NKCA 50/1 Percent Release	LAB	C	--	AGE,RACE, OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM
NKCI 50/1 Net Response (cpm)	LAB	C	--	AGE,RACE OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM

TABLE 19-2. (continued)

Statistical Analysis for the Immunologic Evaluation

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
NKCI 50/1 Percent Release	LAB	C	--	AGE,RACE OCC,PACKYR, CSMOK,DRKYR, ALC,BATCH, DAY(BATCH)	UC:GLM AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Age (AGE)	MIL	D/C	Born ≥1942 Born 1923-1941 Born ≤1922
Race (RACE)	MIL	D	Nonblack Black
Occupation (OCC)	MIL	D	Officer Enlisted Flyer Enlisted Groundcrew
Lifetime Cigarette Smoking History (PACKYR) (pack-years)	Q-SR	D/C	0 >0-10 >10
Current Cigarette Smoking (CSMOK)(cigarettes/day)	Q-SR	D/C	0-Never 0-Former >0-20 >20
Lifetime Alcohol History (DRKYR) (drink-years)	Q-SR	D/C	0 >0-40 >40

TABLE 19-2. (continued)

Statistical Analysis for the Immunologic Evaluation

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Current Alcohol Use (ALC) (drinks/day)	Q-SR	D/C	0-1 >1-4 >4
Batch-to-Batch (BATCH)	LAB	D	1, 2, 3, ... 80
Blood Draw Day-to-Day [DAY(BATCH)]	LAB	D	1, 2 (actual day dependent on batch)
Mitogen Concentration (CONC)	LAB	D	1, 2, 3
Mitogen Harvest Day (DAY)	LAB	D	1, 2

Abbreviations:

Data Source:
LAB--1987 SIRL laboratory results
MIL--Air Force military records
PE--1987 SCRF physical examination
Q-SR--1987 NORC questionnaire (self-reported)

Data Form:
D--Discrete analysis only
C--Continuous analysis only
D/C--Appropriate form for analysis (either discrete or continuous)

Statistical Analyses:
UC--Unadjusted core analyses
AC--Adjusted core analyses
CA--Dependent variable-covariate associations
UE--Unadjusted exposure index analyses
AE--Adjusted exposure index analyses
L--Longitudinal analyses

Statistical Methods:
CC--Pearson's product moment correlation coefficient
CS--Chi-square contingency table test
FT-Fisher's exact test
GLM--General linear models analysis
LR--Logistic regression analysis
RM--Repeated measures analysis (longitudinal)
TT--Two-sample t-test

and blood draw day, the analyses labeled "unadjusted" and the covariate associations with each dependent variable were adjusted for batch on all cell surface marker and functional stimulation variables, and for blood draw day on these same variables except the CD2, CD4, and CD8 cell counts.

Table 19-2 summarizes the statistical analyses performed for the 1987 immunologic evaluation. The first part of the table describes the dependent variables analyzed. The second part of the table provides a further description of candidate covariates examined. Abbreviations are used extensively in the body of the table and are defined in footnotes.

Table 19-3 gives the frequencies of the participants in each exposure group who had the immunologic and skin tests. The table shows that 478 participants received both the immunologic tests and the skin test, 1,405 received the skin test but not the immunologic tests, 409 participants received the immunologic tests but not the skin tests, and 2 received neither test because of participant refusal.

Data for four participants (two Ranch Hands and two Comparisons) were judged clinically unreasonable and excluded prior to analysis. Some participants were excluded for medical reasons in the immunologic evaluation as stated above, and some dependent variable and covariate data were missing. Table 19-4 summarizes number of participants excluded for medical reasons and number of participants with missing data, by variable and group. Variables used to evaluate skin and immunologic testing are detailed separately in this table, since different subsets of participants received these two types of tests. Skin testing was scheduled for 803 Ranch Hands and 1,080 Comparisons, while 390 Ranch Hands and 497 Comparisons were selected for immunologic testing. The quantitative immunoglobulin testing was based on the entire study population.

RESULTS

Ranch Hand and Comparison Group Contrast

Following quality control concerns over the 1985 skin test data, stringent protocols were established to ensure consistent methods and interpretation. Concordance between readers and duplicate interpretations by the same reader was 92 percent. Over 99.6 percent of the sample population had interpretable skin tests.

Physical Examination Data

Unadjusted and adjusted group contrasts of the Ranch Hand and Comparison relative frequencies of possibly abnormal readings were performed using the results of the composite skin test diagnosis variable. Tables 19-5 and 19-6 present the unadjusted and adjusted analyses, respectively. Table P-2 of Appendix P summarizes the dependent variable-covariate associations. The summary of group-by-covariate interactions is provided in Appendix Table P-3.

TABLE 19-3.

Frequencies and Percentages of Participants Who Took the Immunologic Tests and the Skin Tests by Group

Skin Test	Immunologic Tests	Group					
		Ranch Hand		Comparison		Total	
		Number	Percent	Number	Percent	Number	Percent
Yes	Yes	198	19.9	280	21.6	478	20.8
	No	605	60.8	800	61.6	1,405	61.2
	Total	803	80.7	1,080	83.1	1,883	82.1
No	Yes	192	19.3	217	16.7	409	17.8
	No	0	0.0	2	0.2	2	0.1
	Total	192	19.3	219	16.9	411	17.9

TABLE 19-4.

Number of Participants Excluded and With Missing Data for the Immunologic Assessment by Group

Variable	Analysis Use	Group: Ranch Hand	Group: Comparison	Total
Skin Test Analyses[a]				
Composite Skin Test Diagnosis*	DEP	22	32	54
Current Alcohol Use	COV	5	1	6
Lifetime Alcohol History	COV	10	2	12
Chemotherapy	EXC	0	4	4
X-Ray Treatment	EXC	1	4	5
Anti-Inflammatory or Immunosuppressant Medication	EXC	22	39	61
Examination Group 2	EXC	13	18	31
Quantitative Immunoglobulins[b]				
IgG	DEP	2	2	4
IgA	DEP	2	2	4
IgM	DEP	3	3	6
Current Alcohol Use	COV	5	1	6
Lifetime Alcohol History	COV	10	3	13
Chemotherapy	EXC	0	4	4
X-Ray Treatment	EXC	1	4	5
Anti-Inflammatory or Immunosuppressant Medication	EXC	30	49	79
Immunologic Test Analyses[c]				
CD2 Cells	DEP	3	6	9
CD4 Cells	DEP	3	1	4

TABLE 19-4. (continued)

Number of Participants Excluded and With Missing Data for the Immunologic Assessment by Group

Variable	Analysis Use	Group: Ranch Hand	Group: Comparison	Total
CD8 Cells	DEP	4	1	5
CD20 Cells	DEP	2	1	3
CD25 Cells	DEP	1	3	4
HLA-DR Cells	DEP	0	1	1
CD4/CD8 Ratio	DEP	5	1	6
Unstimulated PHA Response (day 1)	DEP	2	5	7
Unstimulated PHA Response (day 2)	DEP	7	5	12
PHA Net Response (day 1, all concentrations)	DEP	4	4	8
PHA Net Response (day 2, all concentrations)	DEP	8	6	14
Overall PHA Net Response	DEP	12	10	22
Maximum PHA Net Response	DEP	12	10	22
Unstimulated MLC Response	DEP	7	10	17
MLC Net Response	DEP	7	10	17
NKCA 50/1 Net Response	DEP	7	11	18
NKCA 50/1 Percent Release	DEP	7	11	18
NKCI 50/1 Net Response	DEP	6	5	11
NKCI 50/1 Percent Release	DEP	6	5	11
Current Alcohol Use	COV	1	1	2
Lifetime Alcohol History	COV	1	2	3

TABLE 19-4. (continued)

Number of Participants Excluded and With Missing Data for the Immunologic Assessment by Group

Variable	Analysis Use	Group: Ranch Hand	Group: Comparison	Total
Chemotherapy	EXC	0	2	2
X-Ray Treatment	EXC	1	0	1
Anti-Inflammatory or Immunosuppressant Medication	EXC	12	18	30

Abbreviations: DEP--Dependent variable (missing data)
COV--Covariate (missing data)
EXC--Exclusion

*Includes 46 participants who refused and 8 equivocal results.

[a]Scheduled for 803 Ranch Hands and 1,080 Comparisons.

[b]Performed on 995 Ranch Hands and 1299 Comparisons.

[c]Performed on 390 Ranch Hands and 497 Comparisons.

TABLE 19-5.

Unadjusted Analysis for the Composite Skin Test Diagnosis by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Est. Relative Risk (95% C.I.)	p-Value
Composite Skin Test Diagnosis	n	748	987		
	Number/% Abnormal	51 6.8%	41 4.2%	1.69 (1.11,2.58)	0.019
	Normal	697 93.2%	946 95.8%		

TABLE 19-6.

Adjusted Analysis for the Composite Skin Test Diagnosis by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Composite Skin Test Diagnosis	n	743	987	1.73 (1.13,2.64)**	0.011**	GRP*PACKYR (p=0.032) RACE*ALC (p=0.014)

**Group-by-covariate interaction ($0.01<p\leq0.05$)--adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Composite Skin Test Diagnosis

The two groups differed significantly (p=0.019) on the unadjusted group contrast of the composite skin test diagnosis. The Ranch Hand group had a significantly higher relative frequency of participants with possibly abnormal composite skin tests than did the Comparisons (6.8% vs. 4.2%). This difference had an estimated relative risk of 1.69 (95% C.I.: [1.11,2.58]).

There were no significant covariate associations with the composite test diagnosis results pooled over group.

The adjusted analysis of the composite skin test diagnosis results contained a significant group-by-lifetime cigarette smoking history interaction (p=0.032). In addition, the adjusted model had a significant race-by-current alcohol use interaction (p=0.014). Because of the group-by-lifetime cigarette smoking history interaction, group contrasts were performed within each of the following lifetime cigarette smoking categories: never smoked, smoked at most 10 pack-years, and smoked over 10 pack-years. Appendix Table P-3 shows that the group contrasts for the first two categories were not significant (p=0.497 and p=0.590, respectively). For participants who smoked over 10 pack-years, the group contrast was significant (p=0.005). Ranch Hands had a greater frequency of individuals with possibly abnormal skin test results than the Comparisons (7.8% vs. 3.1%). The adjusted relative risk for this difference was 2.66 (95% C.I.: [1.35,5.27]). Following deletion of the group-by-lifetime cigarette smoking history interaction, the group contrast was significant (p=0.011) with an adjusted relative risk of 1.73 (95% C.I.: [1.13,2.64]).

Laboratory Examination Data: Quantitative Studies--Cell Surface Marker (Phenotypic) Studies

For the cell surface marker studies, the following eight variables were analyzed: CD2 cells, CD4 cells, CD8 cells, CD20 cells, CD14 cells, CD25 cells, HLA-DR cells, and CD4/CD8 ratio. The unadjusted and adjusted analyses (summarized in Tables 19-7 and 19-8, respectively) were performed on the natural logarithm of the cell counts (i.e., the natural logarithm of cells/mm^3). Table P-2 of Appendix P summarizes the dependent variable-covariate associations. The summary of group-by-covariate interactions is provided in Appendix P, Table P-3. [Ranges for cell marker variables from SIRL based on both male (40%) and female (60%) lab employees are as follows: CD2 (877-2,452); CD4 (433-1,276); CD8 (283-1,035); CD20 (63-255); CD14 (15-99); CD25 (0-56); HLA-DR (277-796); CD4/CD8 ratio (0.81-2.39).]

CD2 Cells

For the unadjusted analysis of the CD2 cells, the Ranch Hand and Comparison groups did not differ significantly (p=0.857). This analysis was performed without adjustment for any covariates except the batch-to-batch variation.

The covariate associations with CD2 cells showed significant associations with age (p<0.001), occupation (p=0.042), current cigarette smoking (p<0.001),

TABLE 19-7.

Unadjusted Analysis* for Quantitative Study Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	p-Value
CD2 Cells	n	374	471	
	Mean[a]	1,604.4	1,597.3	0.857
	95% C.I.[a]	(1,544.0, 1,667.2)	(1,544.5, 1,651.9)	
CD4 Cells	n	374	476	
	Mean[a]	904.0	893.6	0.683
	95% C.I.[a]	(864.8,945.0)	(859.7,928.8)	
CD8 Cells	n	373	476	
	Mean[a]	485.7	477.7	0.632
	95% C.I.[a]	(460.2,512.6)	(455.8,500.7)	
CD20 Cells	n	375	476	
	Mean[a]	155.2	151.8	0.576
	95% C.I.[a]	(146.1,164.9)	(144.1,160.0)	
CD14 Cells	n	377	477	
	Mean[a]	31.2	31.7	0.731
	95% C.I.[a]	(28.7,33.8)	(29.6,34.1)	
CD25 Cells[b]	n	268	340	
	Mean[a]	12.0	12.9	0.362
	95% C.I.[a]	(10.5,13.6)	(11.6,14.4)	
	n	376	474	
	Number/%			
	0	108 28.7%	134 28.3%	0.944
	>0	268 71.3%	340 71.7%	
HLA-DR Cells	n	377	476	
	Mean[a]	435.6	423.4	0.327
	95% C.I.[a]	(416.6,455.5)	(407.4,440.1)	

TABLE 19-7. (continued)

Unadjusted Analysis* for Quantitative Study Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	p-Value
CD4/CD8 Ratio	n	372	476	
	Mean[a]	1.84	1.88	0.537
	95% C.I.[a]	(1.75,1.94)	(1.80,1.97)	
TLC	n	377	477	
	Mean[a]	2,008	1,983	0.790
	95% C.I.[a]	(1,943,2,075)	(1,925,2,042)	
IgG	n	963	1243	
	Mean	1,036.1	1,048.8	0.205
	95% C.I.	(1,020.7,1,051.6)	(1,035.9,1,061.8)	
IgA	n	963	1,243	
	Mean[a]	207.29	210.55	0.406
	95% C.I.	(201.29,213.47)	(205.54,215.69)	
IgM	n	962	1,242	
	Mean[a]	111.20	110.79	0.855
	95% C.I.[a]	(107.90,114.59)	(107.87,113.78)	

*The CD2, CD4, and CD8 cell surface markers variables were adjusted only for batch-to-batch variation. The other cell surface marker variables were adjusted for both batch-to-batch and blood draw day-to-day variation.

[a]Transformed from natural logarithm scale.

[b]CD25 cell counts contained both zero values and positive values. Groups are compared on mean of positive CD25 cell counts and on proportion of zero CD25 cell counts.

TABLE 19-8.

Adjusted Analysis for Quantitative Study Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	p-Value	Covariate Remarks
CD2 Cells	n	373	469		BATCH (p=0.051)
	Adj. Mean[a]	1,621.4	1,602.0	0.610	AGE*DRKYR (p=0.004)
	95% C.I.[a]	(1,561.2, 1,683.9)	(1,549.0, 1,656.8)		CSMOK*DRKYR (p<0.001) CSMOK*OCC (p=0.040)
CD4 Cells	n	373	474		BATCH (p=0.005)
	Adj. Mean[a]	910.8	891.2	0.411	AGE*DRKYR (p<0.001)
	95% C.I.[a]	(873.8,949.5)	(859.4,924.0)		CSMOK*DRKYR (p<0.001) ALC*DRKYR (p=0.030)
CD8 Cells	n	373	476		BATCH (p=0.051)
	Adj. Mean[a]	487.2	476.4	0.512	AGE (p=0.009)
	95% C.I.[a]	(461.9,513.9)	(454.8,499.1)		CSMOK (p=0.002)
CD20 Cells	n	374	474		BATCH (p<0.001)
	Adj. Mean[a]	174.3	170.7	0.569	DAY(BATCH) (p=0.002)
	95% C.I.[a]	(158.9,191.1)	(156.2,186.4)		RACE (p=0.034) AGE*CSMOK (p=0.046) ALC*RACE (p=0.032) ALC*DRKYR (p=0.010)
CD14 Cells	n	377	477		BATCH (p<0.001)
	Adj. Mean[a]	28.0	28.6	0.690	DAY(BATCH) (p=0.031)
	95% C.I.[a]	(24.7,31.7)	(25.3,32.2)		RACE (p=0.021) AGE*CSMOK (p=0.008) AGE*PACKYR (p=0.025) CSMOK*PACKYR (p<0.001)
CD25 Cells[b]	n	268	340		BATCH (p<0.001)
	Adj. Mean[a]	12.0	12.9	0.350	DAY(BATCH) (p<0.001)
	95% C.I.[a]	(10.5,13.6)	(11.6,14.4)		CSMOK (p=0.030)
HLA-DR Cells	n	376	474		BATCH (p<0.001)
	Adj. Mean[a]	436.2	423.2	0.268	DAY(BATCH) (p=0.003)
	95% C.I.[a]	(418.2,455.0)	(408.0,438.9)		AGE (p<0.001) CSMOK (p<0.001) ALC (p=0.027) DRKYR (p=0.022)
CD4/CD8 Ratio	n	371	475		BATCH (p=0.003)
	Adj. Mean[a]	1.84	1.87	0.707	DAY(BATCH) (p=0.038)
	95% C.I.[a]	(1.74,1.94)	(1.78,1.96)		CSMOK (p=0.031) ALC*OCC (p=0.032)

TABLE 19-8. (continued)

Adjusted Analysis for Quantitative Study Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	p-Value	Covariate Remarks
TLC	n	377	477		BATCH (p<0.001)
	Adj. Mean[a]	2,006	1,982	0.597	DAY(BATCH) (p<0.001)
	95% C.I.[a]	(1,933,2,081)	(1,919,2,047)		AGE (p<0.001)
					CSMOK*OCC (p=0.016)
IgG	n	953	1240		AGE*PACKYR (p<0.001)
	Adj. Mean	1,115.3	1,123.3	0.406	CSMOK*RACE (p=0.046)
	95% C.I.	(1,086.1,1,144.5)	(1,094.7,1,151.8)		PACKYR*RACE (p=0.027)
					DRKYR*PACKYR (p=0.030)
					CSMOK*PACKYR (p=0.012)
IgA	n	953	1240		AGE*CSMOK (p=0.020)
	Adj. Mean[a]	216.76	219.52	0.499	DRKYR*PACKYR (p=0.032)
	95% C.I.[a]	(207.28,226.67)	(210.41,229.02)		
IgM	n	962	1242		
	Adj. Mean[a]	104.23	103.91	0.876	RACE (p<0.001)
	95% C.I.[a]	(99.38,109.33)	(99.31,108.72)		

[a]Transformed from natural logarithm scale.

[b]Groups compared on adjusted means of positive cell counts.

and lifetime cigarette smoking history ($p<0.001$). Average CD2 cell counts decreased with increasing age. Participants born in or after 1942 had a mean CD2 cell count of 1,674.5 cells/mm^3; participants born between 1923 and 1941 had a mean CD2 count of 1,566.9 cells/mm^3; and participants born in or before 1922 had a mean CD2 count of 1,300.6 cells/mm^3. For officers, enlisted flyers, and enlisted groundcrew, the mean CD2 cell counts were 1,538.5 cells/mm^3, 1,652.6 cells/mm^3, and 1,634.0 cells/mm^3, respectively. For current cigarette smoking, the average CD2 cell count for participants who never smoked was 1,490.5 cells/mm^3. For former smokers, the mean CD2 count was 1,506.7 cells/mm^3. For individuals smoking at most 20 cigarettes per day, the mean CD2 count was 1,793.0 cells/mm^3, and for those individuals smoking over 20 cigarettes per day, the mean CD2 count was 1,858.6 cells/mm^3. For lifetime cigarette smoking history, participants who never smoked had a mean CD2 count of 1,491.3 cells/mm^3; those smokers with at most a 10 pack-year history had a mean CD2 count of 1,614.2 cells/mm^3; participants with a lifetime cigarette smoking history over 10 pack-years had an average CD2 cell count of 1,667.4 cells/mm^3.

For the adjusted analysis of CD2 counts, the Ranch Hand and Comparison group contrast was not significant ($p=0.610$). In the adjusted model, the batch-to-batch covariate was marginally significant ($p=0.051$) and the following interactions were significant: age-by-lifetime alcohol history ($p=0.004$), current cigarette smoking-by-lifetime alcohol history ($p<0.001$), and current cigarette smoking-by-occupation ($p=0.040$).

CD4 Cells

The unadjusted analysis of the CD4 counts exhibited no significant difference between the Ranch Hand and Comparison groups ($p=0.683$). This unadjusted group contrast was performed adjusting only for batch-to-batch variation.

The following covariates exhibited significant associations with the CD4 cell counts: age ($p<0.001$), occupation ($p=0.030$), current cigarette smoking ($p<0.001$), lifetime cigarette smoking history ($p<0.001$), and lifetime alcohol history ($p=0.022$). The younger participants, those born in or after 1942, had a mean CD4 count of 955.1 cells/mm^3. Participants born between 1923 and 1941 had an average CD4 count of 872.7 cells/mm^3. The oldest participants, those born in or before 1922, had the lowest average CD4 count of 665.5 cells/mm^3. The enlisted flyers had the highest average CD4 count of 930.1 cells/mm^3, followed by the enlisted groundcrew with an average CD4 count of 922.5 cells/mm^3, and the officers with a CD4 mean value of 855.8 cells/mm^3. For the current cigarette smoking covariate, those participants who never smoked and former smokers had CD4 average counts of 798.8 cells/mm^3 and 835.8 cells/mm^3, respectively. For those participants smoking at most 20 cigarettes per day, the average CD4 count was 1,051.4 cells/mm^3, and for those participants smoking over 20 cigarettes per day, the average CD4 cell count was 1,111.1 cells/mm^3. For lifetime cigarette smoking history, participants who never smoked had a mean CD4 count of 799.8 cells/mm^3. Participants with lifetime smoking values above 0 but not greater than 10 pack-years had a CD4 average of 920.2 cells/mm^3, while those with a lifetime cigarette smoking value over 10 pack-years had an average CD4 cell count of 955.0 cells/mm^3. For lifetime alcohol history, nondrinkers had a mean CD4 count of 804.7

cells/mm^3. Participants with lifetime alcohol values above 0 but not above 40 drink-years had an average CD4 count of 897.9 cells/mm^3. Those participants having a lifetime alcohol history over 40 drink-years had an average CD4 level of 940.0 cells/mm^3.

The Ranch Hand and Comparison group contrast was not significant ($p=0.411$) for the adjusted analysis of the CD4 counts. In the adjusted model, the batch-to-batch covariate was significant ($p=0.005$). The following interactions were also significant in the adjusted model: age-by-lifetime alcohol history ($p<0.001$), lifetime alcohol history-by-current cigarette smoking ($p<0.001$), and current alcohol use-by-lifetime alcohol history ($p=0.030$).

CD8 Cells

Ranch Hands and Comparisons did not differ significantly on the unadjusted analysis of the CD8 cell counts ($p=0.632$). This unadjusted analysis was adjusted only for batch-to-batch variation.

Significant associations with CD8 cell counts were found for the following covariates: age ($p=0.011$) and current cigarette smoking ($p<0.001$). Participants born in or after 1942 had a mean CD8 cell count of 504.4 cells/mm^3. For those participants born between 1923 and 1941, the average CD8 cell count was 469.3 cells/mm^3. Participants born in or before 1922 had an average CD8 cell count of 396.6 cells/mm^3. For the current cigarette smoking covariate, participants who never smoked and those who formerly smoked had average CD8 counts of 458.8 cells/mm^3 and 457.0 cells/mm^3, respectively. For individuals smoking at most 20 cigarettes per day, the average CD8 count was 523.9 cells/mm^3, and for those smoking over 20 cigarettes per day, the mean CD8 value was 540.4 cells/mm^3.

For the adjusted analysis of the CD8 cell counts, the Ranch Hand and Comparison group contrast was not significant ($p=0.512$). Age and current cigarette smoking were significant covariates for the adjusted model ($p=0.009$ and $p=0.002$, respectively), and the batch-to-batch covariate was marginally significant ($p=0.051$).

CD20 Cells

Ranch Hands and Comparisons did not differ significantly on the unadjusted analysis of the CD20 cell counts ($p=0.576$). The only covariates used for this analysis were batch-to-batch and blood draw day-to-day variation.

The covariates of age ($p<0.001$), race ($p=0.002$), occupation ($p<0.001$), current cigarette smoking ($p<0.001$), and lifetime cigarette smoking history ($p=0.025$) exhibited significant associations with the CD20 cell counts. Current alcohol use exhibited a borderline significant association with CD20 cells ($p=0.053$). Average CD20 cell counts decreased with increasing age. For participants born in or after 1942, the mean CD20 cell count was 170.4 cells/mm^3. Participants born between 1923 and 1941 had a CD20 cell count average of 144.1 cells/mm^3. Participants born in or before 1922 had an

average CD20 cell count of 105.7 cells/mm^3. For Blacks, the average CD20 cell count was 198.5 cells/mm^3 versus 151.3 cells/mm^3 for nonblacks. The enlisted groundcrew had the highest mean CD20 count with a value of 164.0 cells/mm^3. The enlisted flyers were next highest with an average CD20 value of 159.1 cells/mm^3. Officers had the lowest CD20 mean at 139.0 cells/mm^3. For current cigarette smoking, participants who never smoked and those who were former smokers had average CD20 cell counts of 139.6 cells/mm^3 and 138.1 cells/mm^3, respectively. For smoking participants who did not exceed 20 cigarettes per day, the average CD20 value was 186.9 cells/mm^3. For those individuals smoking more than 20 cigarettes per day, the mean CD20 value was 186.6 cells/mm^3. For the lifetime smoking history covariate, participants with more than 10 pack-years smoking had the highest average CD20 cell count of 160.2 cells/mm^3. For individuals with no more than 10 pack-years of smoking, the average CD20 cell count was 156.4 cells/mm^3. For the nonsmokers, the CD20 average was 140.8 cells/mm^3. For current alcohol use, the average CD20 cell count decreased as alcohol use increased. For participants having at most one drink per day, the average CD20 count was 155.6 cells/mm^3. Those participants having more than one but not more than four drinks per day had an average CD20 count of 145.7 cells/mm^3. Participants imbibing over four drinks per day had an average CD20 cell count of 122.4 cells/mm^3.

For the adjusted analysis of the CD20 cell counts, Ranch Hands and Comparisons did not differ significantly ($p=0.569$). Significant covariates in the adjusted model were batch-to-batch variation ($p<0.001$), blood draw day-to-day variation ($p=0.002$), and race ($p=0.034$). Significant covariate interactions were age-by-current cigarette smoking ($p=0.046$), current alcohol use-by-race ($p=0.032$), and current alcohol use-by-lifetime alcohol history ($p=0.010$).

CD14 Cells

The unadjusted analysis of the CD14 cell counts did not exhibit a significant group difference ($p=0.731$). This contrast was performed without adjustment for any of the covariates, except batch-to-batch variation and blood draw day-to-day variation.

Significant covariate associations with CD14 cell counts were found for race ($p=0.006$), current cigarette smoking ($p<0.001$), lifetime cigarette smoking history ($p<0.001$), and current alcohol use ($p=0.020$). Lifetime alcohol history displayed a borderline significant association ($p=0.082$). Nonblack participants had a higher average CD14 cell count than the Black participants (32.0 cells/mm^3 vs. 23.2 cells/mm^3). Based on the current cigarette smoking covariate, participants who never smoked or were former smokers had average CD14 cell counts of 26.0 cells/mm^3 and 28.7 cells/mm^3, respectively. Those participants who smoked at most 20 cigarettes per day had an average CD14 cell count of 40.1 cells/mm^3. Participants who smoked more than 20 cigarettes per day had an average CD14 cell count of 43.1 cells/mm^3. Based on the lifetime cigarette smoking history covariate, CD14 average values increased as number of pack-years increased. Individuals with a lifetime cigarette smoking value of zero pack-years had an average CD14 count of 26.2 cells/mm^3. Smokers not exceeding 10 pack-years had a CD14 average cell count of 29.9 cells/mm^3. Those smokers having a lifetime cigarette smoking

covariate value over 10 pack-years had an average CD14 value of 36.7 cells/mm^3. For the current alcohol use covariate, the participants having over four drinks per day had higher CD14 cell counts (44.0 cells/mm^3) than either the moderate or lighter drinking participants (34.5 cells/mm^3 and 30.6 cells/mm^3, respectively). For lifetime alcohol history, nondrinkers had an average CD14 value of 31.5 cells/mm^3. Participants having a drink-year total of 40 or less had an average CD14 cell count of 30.5 cells/mm^3. Participants with more than 40 drink-years had an average CD14 of 35.2 cells/mm^3.

The adjusted analysis of the CD14 cell counts did not exhibit a significant group difference between the Ranch Hand and Comparison groups ($p=0.690$). Significant covariates for this adjusted analysis were batch-to-batch variation ($p<0.001$), blood draw day-to-day variation ($p=0.031$), and race ($p=0.021$). In addition, the following covariate interactions were significant in the model: age-by-current cigarette smoking ($p=0.008$), age-by-lifetime cigarette smoking history ($p=0.025$), and current cigarette smoking-by-lifetime cigarette smoking history ($p<0.001$).

CD25 Cells

Because the CD25 cell counts contained a substantial number of zero values, the unadjusted analysis was performed in two parts: Ranch Hands and Comparisons were compared on the proportions of zero cell counts and on the mean number of CD25 cells for the nonzero CD25 cell counts. Ranch Hands and Comparisons did not differ on the proportion of zero value cell counts ($p=0.944$). For the unadjusted analysis of the nonzero CD25 cell counts, the group contrast of the mean cell counts was not significant ($p=0.362$). For the latter unadjusted analysis, the only covariates used for adjustment were batch-to-batch and blood draw day-to-day variation.

A borderline significant relationship between nonzero CD25 cell counts and age was found ($p=0.081$). Younger participants had higher nonzero CD25 cell count averages than older participants. For individuals born in or after 1942, the nonzero CD25 cell count average was 13.3 cells/mm^3. For those born in the interval 1923 to 1941, the nonzero CD25 cell count average decreased to 12.4 cells/mm^3. For those individuals born in or before 1922, the nonzero CD25 average count decreased to 8.1 cells/mm^3.

An adjusted analysis of the proportion of zero value CD25 cell counts was not performed because of the highly nonsignificant unadjusted analysis found earlier. For the adjusted analysis of the nonzero CD25 cell counts, Ranch Hands and Comparisons did not differ significantly ($p=0.350$). For the adjusted model, the batch-to-batch covariate, blood draw day-to-day covariate, and current cigarette smoking were significant ($p<0.001$, $p<0.001$, and $p=0.030$, respectively).

HLA-DR Cells

For the unadjusted analysis of the HLA-DR cells, no significant group difference was found ($p=0.327$). The only covariates used in this analysis were batch-to-batch and blood draw day-to-day variation.

For the HLA-DR cells, age ($p<0.001$), occupation ($p=0.005$), current cigarette smoking ($p<0.001$), and lifetime cigarette smoking history ($p<0.001$) exhibited significant covariate associations. Averages for the HLA-DR cell counts decreased with increasing age. For those individuals born in or after 1942, the average HLA-DR was 450.1 cells/mm^3. Older individuals, born between 1923 and 1941, had a lower average HLA-DR value of 418.0 cells/mm^3. Those participants born in or before 1922 had the lowest HLA-DR average value at 346.9 cells/mm^3. For enlisted flyers, the average HLA-DR cell count was 448.1 cells/mm^3, as compared to 443.6 cells/mm^3 for the enlisted groundcrew and 402.5 cells/mm^3 for the officers. For the current cigarette smoking covariate, those who never smoked had the lowest HLA-DR average at 378.8 cells/mm^3. Former smokers had a higher HLA-DR average value of 396.9 cells/mm^3. Those individuals not smoking over 20 cigarettes per day had a higher HLA-DR average at 515.6 cells/mm^3. Smokers over 20 cigarettes per day also had a higher HLA-DR average at 527.6 cells/mm^3. Based on the lifetime cigarette smoking history covariate, the average HLA-DR cell count increased as number of pack-years increased. For nonsmokers, the average HLA-DR cell count was 381.3 cells/mm^3. Smokers with at most a 10 pack-year value for this covariate had an HLA-DR average of 427.9 cells/mm^3. Those smokers with over 10 pack-years lifetime cigarette smoking history had an average HLA-DR cell count of 463.4 cells/mm^3.

The adjusted group contrast of Ranch Hands and Comparisons was not significant ($p=0.268$) for the HLA-DR cell counts. This adjusted analysis had the following significant covariates in the model: batch-to-batch variation ($p<0.001$), blood draw day-to-day variation ($p=0.003$), age ($p<0.001$), current cigarette smoking ($p<0.001$), current alcohol use ($p=0.027$), and lifetime alcohol history ($p=0.022$).

CD4/CD8 Ratio

No group difference was found for the unadjusted analysis of the CD4/CD8 ratio ($p=0.537$). Only the covariates of batch-to-batch and blood draw day-to-day variation were used.

Current cigarette smoking and lifetime cigarette smoking history exhibited significant associations with the CD4/CD8 ratio ($p=0.043$ and $p=0.041$, respectively). Lifetime alcohol history also displayed a significant covariate relation with CD4/CD8 ratio ($p=0.050$). For current cigarette smoking, the participants who never smoked or were former smokers had average CD4/CD8 ratios of 1.75 and 1.86, respectively. Smokers not exceeding 20 cigarettes per day had an average CD4/CD8 ratio of 2.00, and those individuals smoking more than 20 cigarettes per day had an average CD4/CD8 ratio of 1.97. Based on lifetime cigarette smoking history, nonsmokers had an average CD4/CD8 ratio of 1.75. Smokers at or below 10 pack-years had an average CD4/CD8 ratio of 1.97, and those smokers with more than 10 pack-years had an average CD4/CD8 ratio of 1.89. For the lifetime alcohol history covariate, the average CD4/CD8 ratio increased as number of drink-years increased. For lifetime nondrinkers, the average CD4/CD8 ratio was 1.73. For those individuals with at most 40 drink-years on lifetime alcohol history, the average CD4/CD8 ratio increased to 1.85, and for those over 40 drink-years the average CD4/CD8 ratio increased to 2.01.

For the adjusted analysis of the CD4/CD8 ratio, the Ranch Hand and Comparison group contrast was not significant (p=0.707). Significant covariate terms in the adjusted model were the batch-to-batch and blood draw day-to-day covariates (p=0.003 and p=0.038, respectively) and current cigarette smoking (p=0.031). The interaction of current alcohol use-by-occupation was also significant (p=0.032).

Laboratory Examination Data: Quantitative Studies--TLC

The results of the unadjusted analyses, as presented in Table 19-7, showed that the Ranch Hand and Comparison group contrast was not significant (p=0.790). Only the batch-to-batch and blood draw day-to-day covariates were used in this analysis.

As shown in Table P-2 of Appendix P, age (p<0.001), occupation (p=0.016), current cigarette smoking (p<0.001), and lifetime cigarette smoking history (p=0.001) exhibited significant covariate associations with TLC. The mean TLC decreased with age (2,066.5 cells/mm^3 for those born in or after 1942, 1,966.7 cells/mm^3 for those born between 1923 and 1941, and 1,651.5 cells/mm^3 for those born in or before 1922). For occupation, the highest mean TLC was in the enlisted flyers (2,065.6 cells/mm^3). The mean counts for the officers and enlisted groundcrew were 1,905.1 cells/mm^3 and 2,041.5 cells/mm^3, respectively. The mean TLC was also found to have increased with increasing levels of both current and lifetime cigarette smoking. For current cigarette smoking, the nonsmokers had a mean TLC of 1,849.7 cells/mm^3, as compared to means of 1,862.5 cells/mm^3 for former smokers, 2,251.5 cells/mm^3 for moderate smokers, and 2,323.2 cells/mm^3 for heavy smokers. Based on lifetime cigarette smoking history, the mean counts were 1,849.7 cells/mm^3, 2,008.3 cells/mm^3, and 2,073.4 cells/mm^3 for nonsmokers, moderate smokers, and heavy smokers, respectively.

No significant difference between the two groups was detected in the adjusted analysis (p=0.597). Age, batch-to-batch, and blood draw day-to-day variation were significant covariates in the adjusted model (p<0.001 for each). The model also contained a significant occupation-by-current cigarette smoking interaction (p=0.016). The results are presented in Table 19-8.

Laboratory Examination Data: Quantitative Studies--Quantitative Immunoglobulins

Tables 19-7 and 19-8 present the results of unadjusted and adjusted analyses, respectively, for IgG, IgA, and IgM. Table P-2 of Appendix P summarizes the dependent variable-covariate associations for these variables.

IgG

No group difference was found in the unadjusted analysis of IgG (p=0.205).

Significant associations with IgG were found for age (p=0.028), race (p<0.001), occupation (p<0.001), current cigarette smoking (p<0.001), lifetime

cigarette smoking history ($p<0.001$), current alcohol use ($p=0.043$), and lifetime alcohol history ($p=0.040$).

The mean IgG was 1,054.7 mg/dl for those born in or after 1942, as compared to means of 1,032.0 mg/dl and 1,081.7 mg/dl for those born between 1923 and 1941 and those born in or before 1922, respectively. The mean for Blacks was higher than the mean for nonblacks (1,264.2 mg/dl vs. 1,029.1 mg/dl). The enlisted groundcrew had the highest mean (1,067.6 mg/dl), followed by the enlisted flyers (1,027.9 mg/dl) and the officers (1,020.8 mg/dl).

The mean IgG decreased with smoking intensity for both current and lifetime cigarette smoking. For current smoking, the nonsmokers had a mean of 1,094.2 mg/dl, as compared to means of 1,043.4 mg/dl, 1,015.5 mg/dl, and 986.3 mg/dl for former, moderate, and heavy smokers, respectively. Based on lifetime cigarette smoking history, the nonsmokers had a mean IgG of 1,094.1 mg/dl. The means for moderate and heavy smokers were 1,041.2 mg/dl and 1,013.4 mg/dl, respectively, based on lifetime cigarette smoking history.

For current alcohol use, the moderate drinkers had the lowest mean IgG (1,016.2 mg/dl). Heavy drinkers had a lower mean than nondrinkers (1,039.0 mg/dl vs. 1,049.2 mg/dl). IgG decreased with lifetime alcohol consumption (1,079.0 mg/dl for nondrinkers, 1,043.8 mg/dl for moderate drinkers, and 1,028.7 mg/dl for heavy drinkers).

In the adjusted analysis, there was no significant difference between the two groups ($p=0.406$). In the adjusted model, there were five significant covariate-by-covariate interactions: age-by-lifetime cigarette smoking history ($p<0.001$), race-by-current cigarette smoking ($p=0.046$), race-by-lifetime cigarette smoking history ($p=0.027$), lifetime alcohol history-by-lifetime cigarette smoking history ($p=0.030$), and current cigarette smoking-by-lifetime cigarette smoking history ($p=0.012$).

IgA

In the unadjusted analysis of IgA, no significant difference between the Ranch Hands and Comparisons was detected ($p=0.406$).

The covariate tests for IgA revealed significant or borderline significant associations with race ($p=0.035$), occupation ($p=0.070$), current alcohol use ($p=0.060$), lifetime alcohol history ($p=0.003$), and current cigarette smoking ($p=0.032$). Blacks had a higher mean IgA than nonblacks (226.06 mg/dl vs. 208.08 mg/dl). Of the three occupational categories, the officers had the lowest mean (203.56 mg/dl), followed by the enlisted flyers (210.24 mg/dl) and the enlisted groundcrew (213.40 mg/dl). IgA decreased with smoking intensity based on current smoking patterns (213.46 mg/dl for nonsmokers, 211.81 mg/dl for former smokers, 208.03 mg/dl for moderate smokers, and 196.97 mg/dl for heavy smokers). IgA increased with increasing alcohol consumption based on current alcohol use and lifetime alcohol history. For current alcohol use, the means were 207.36 mg/dl, 213.07 mg/dl, and 232.37 mg/dl for nondrinkers, moderate drinkers, and heavy drinkers, respectively. Based on lifetime alcohol history, the nondrinkers had a mean of 197.06 mg/dl, as compared to means of 207.24 mg/dl and 220.52 mg/dl for moderate and heavy drinkers, respectively.

Based on the results of the adjusted analysis of IgA, no significant difference between the Ranch Hands and Comparisons was revealed (p=0.499). Age-by-current cigarette smoking and lifetime cigarette smoking history-by-lifetime alcohol history interactions were significant terms in the model (p=0.020 and p=0.032, respectively).

IgM

Based on the unadjusted analysis of IgM, there was no significant difference between the two groups (p=0.855).

Significant associations for IgM were detected for race and current alcohol use (p<0.001 and p=0.011, respectively). The association with age was marginally significant (p=0.088). IgM decreased with age (113.80 mg/dl for those born in or after 1942, 109.09 mg/dl for those born between 1923 and 1941, and 106.58 mg/dl for those born in or before 1922). Nonblacks had a higher mean than Blacks (111.95 mg/dl vs. 96.70 mg/dl). IgM was found to increase with current alcohol use. The nondrinkers had a mean of 110.08 mg/dl, as compared to means of 111.91 mg/dl and 129.93 mg/dl for moderate and heavy drinkers, respectively.

The adjusted analysis of IgM also did not detect a significant group difference (p=0.876). Race was a significant covariate in the adjusted model (p<0.001).

Laboratory Examination Data: Functional Stimulation Tests

Tables 19-9 and 19-10 summarize unadjusted and adjusted group contrasts for the functional stimulation studies of PHA, MLC, NKCA, and NKCI. Table P-2 of Appendix P summarizes the dependent variable-covariate associations. The summary of group-by-covariate interactions is provided in Appendix Table P-3.

The following PHA response variables were analyzed: unstimulated PHA responses for day 1 and day 2 concurrently, six PHA net responses for each of two harvest days at three mitogen concentration levels, an overall simultaneous analysis of the six PHA net responses, and the maximum of the six PHA net responses over day and concentration level. Analyses for the two unstimulated PHA variables were performed on the natural logarithm of the cell counts (i.e., the natural logarithm of cpm). No transformations were used for the analyses of the PHA net response variables.

For the MLC test, analyses were performed on an unstimulated MLC response and a MLC net response. Analyses of the unstimulated MLC variable were based on the natural logarithm of the counts (in cpm). The MLC net responses were analyzed without transformation.

For the natural killer cell assays, the following variables were analyzed: NKCA 50/1 net response (cpm), NKCA 50/1 percent release, NKCI 50/1 net response (cpm), and NKCI 50/1 percent release. These variables were analyzed without transformation.

TABLE 19-9.

Unadjusted Analysis* for Functional Stimulation Test Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	p-Value
Unstimulated PHA Response	n	368	468	0.840
	Mean[a]	1,965	1,979	
	95% C.I.[a]	(1,869, 2,067)	(1,894, 2,067)	
PHA Net Response (day 1, concentration 1)	n	373	473	0.915
	Mean	100,142	100,483	
	95% C.I.	(95,221, 105,064)	(96,229, 104,737)	
PHA Net Response (day 1, concentration 2)	n	373	473	0.976
	Mean	160,626	160,741	
	95% C.I.	(154,885, 166,368)	(155,778, 165,703)	
PHA Net Response (day 1, concentration 3)	n	373	473	0.538
	Mean	147,511	145,368	
	95% C.I.	(142,139, 152,883)	(140,723, 150,012)	
PHA Net Response (day 2, concentration 1)	n	369	471	0.337
	Mean	159,602	162,849	
	95% C.I.	(154,389, 164,816)	(158,326, 167,372)	
PHA Net Response (day 2, concentration 2)	n	369	471	0.511
	Mean	179,173	181,369	
	95% C.I.	(174,023, 184,324)	(176,900, 185,837)	
PHA Net Response (day 2, concentration 3)	n	369	471	0.886
	Mean	127,510	127,034	
	95% C.I.	(122,385, 132,635)	(122,587, 131,480)	
Overall PHA Net Response	n	365	467	0.841
	Mean	145,509	146,038	
	95% C.I.	(141,429, 149,589)	(142,511, 149,566)	

TABLE 19-9. (continued)

Unadjusted Analysis* for Functional Stimulation Test Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	p-Value
Maximum PHA Net Response	n	365	467	0.506
	Mean	205,322	205,072	
	95% C.I.	(197,898, 212,745)	(198,826, 211,318)	
Unstimulated MLC Response	n	370	467	0.221
	Mean[a]	4,067	3,813	
	95% C.I.[a]	(3,752, 4,409)	(3,554, 4,091)	
MLC Net Response	n	370	467	0.647
	Mean	87,966	86,693	
	95% C.I.	(83,709, 92,223)	(82,980, 90,406)	
NKCA 50/1 Net Response	n	370	467	0.435
	Mean	410.6	420.9	
	95% C.I.	(390.2,430.9)	(403.1,438.8)	
NKCA 50/1 Percent Release	n	370	467	0.569
	Mean	35.2	35.8	
	95% C.I.	(33.5,36.8)	(34.3,37.2)	
NKCI 50/1 Net Response	n	371	472	0.462
	Mean	807.5	813.2	
	95% C.I.	(795.4,819.5)	(802.8,823.6)	
NKCI 50/1 Percent Release	n	371	472	0.270
	Mean	66.4	67.1	
	95% C.I.	(65.5,67.4)	(66.3,67.9)	

*Adjusted for batch-to-batch variation and blood draw day-to-day variation.

[a]Transformed from natural logarithm scale.

TABLE 19-10.

Adjusted Analysis for Functional Stimulation Test Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	p-Value	Covariate Remarks
Unstimulated PHA Response	n	367	466		BATCH (p<0.001)
	Adj. Mean[a]	2,182	2,176	0.933	DAY(BATCH) (p=0.021)
	95% C.I.[a]	(2,017, 2,361)	(2,018, 2,347)		AGE (p<0.001)
					RACE (p=0.001)
					ALC*CSMOK (p=0.007)
					ALC*DRKYR (p=0.039)
PHA Net Response (day 1, concentration 1)	n	372	472		GRP*ALC (p=0.042)
	Adj. Mean**	107,678	106,996	0.817**	BATCH (p<0.001)
	95% C.I.**	(99,934, 115,423)	(99,522, 114,411)		DAY(BATCH) (p<0.001)
					AGE (p<0.001)
					RACE (p=0.008)
					OCC (p=0.012)
PHA Net Response (day 1, concentration 2)	n	373	473		BATCH (p<0.001)
	Adj. Mean	169,663	167,524	0.540	DAY(BATCH) (p<0.001)
	95% C.I.	(160,525, 178,801)	(158,712, 176,335)		CSMOK (p=0.044)
					AGE*RACE (p=0.044)
PHA Net Response (day 1, concentration 3)	n	372	472		BATCH (p<0.001)
	Adj. Mean	152,113	147,780	0.185	DAY(BATCH) (p<0.001)
	95% C.I.	(141,773, 162,454)	(137,597, 157,963)		AGE*RACE (p=0.048)
					AGE*ALC (p=0.035)
					RACE*PACKYR (p=0.043)
PHA Net Response (day 2, concentration 1)	n	369	471		BATCH (p<0.001)
	Adj. Mean	160,389	162,777	0.474	DAY(BATCH) (p<0.001)
	95% C.I.	(151,973, 168,805)	(154,582, 170,972)		AGE (p<0.001)
					OCC (p=0.004)
					RACE*CSMOK (p=0.015)
PHA Net Response (day 2, concentration 2)	n	369	471		BATCH (p<0.001)
	Adj. Mean	179,568	180,306	0.820	DAY(BATCH) (p<0.001)
	95% C.I.	(174,573, 184,563)	(175,966, 184,645)		AGE*PACKYR (p=0.027)
PHA Net Response (day 2, concentration 3)	n	369	471		BATCH (p<0.001)
	Adj. Mean	136,095	134,758	0.683	DAY(BATCH) (p<0.001)
	95% C.I.	(128,066, 144,124)	(127,088, 142,428)		AGE (p<0.001)
					RACE (p=0.009)

TABLE 19-10. (continued)

Adjusted Analysis for Functional Stimulation Test Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	p-Value	Covariate Remarks
Overall PHA Net Response	n	364	466		BATCH (p<0.001)
	Adj. Mean	151,983	151,085	0.720	DAY(BATCH) (p<0.001)
	95% C.I.	(145,766, 158,199)	(145,158, 157,012)		RACE (p=0.014) AGE*ALC (p=0.035)
Maximum PHA Net Response	n	365	467		BATCH (p<0.001)
	Adj. Mean	203,157	203,488	0.914	DAY(BATCH) (p<0.001)
	95% C.I.	(198,322, 207,991)	(199,298, 207,679)		AGE (p<0.001) CSMOK (p=0.006)
Unstimulated MLC Response	n	369	467		BATCH (p<0.001)
	Adj. Mean[a]	4,971	4,590	0.116	DAY(BATCH) (p=0.027)
	95% C.I.[a]	(4,387, 5,633)	(4,073, 5,172)		RACE (p<0.001) AGE*DRKYR (p=0.014)
MLC Net Response	n	370	467		GRP*RACE (p=0.039)
	Adj. Mean**	93,751	92,383	0.617**	BATCH (p<0.001)
	95% C.I.**	(86,960, 100,543)	(85,845, 98,921)		DAY(BATCH) (p<0.001) AGE (p=0.014) OCC (p=0.014) CSMOK*PACKYR (p=0.032)
NKCA 50/1 Net Response	n	369	466		GRP*RACE (p=0.040)
	Adj. Mean**	409.5	418.4	0.494**	BATCH (p<0.001)
	95% C.I.**	(376.2,442.8)	(385.9,450.8)		DAY(BATCH) (p<0.001) RACE*CSMOK (p=0.014) OCC*PACKYR (p=0.004) CSMOK*PACKYR (p=0.041) AGE*ALC (p=0.031)
NKCA 50/1 Percent Release	n	369	466		GRP*RACE (p=0.022)
	Adj. Mean**	35.1	35.5	0.710**	BATCH (p<0.001)
	95% C.I.**	(32.3,37.8)	(32.8,38.1)		DAY(BATCH) (p<0.001) RACE*CSMOK (p=0.006) OCC*PACKYR (p=0.020) AGE*ALC (p=0.034)
NKCI 50/1 Net Response	n	371	472		GRP*RACE (p=0.003)
	Adj. Mean	****	****	****	BATCH (p<0.001)
	95% C.I.	****	****		DAY(BATCH) (p<0.001) RACE*CSMOK (p=0.020) OCC*PACKYR (p=0.031) CSMOK*PACKYR (p=0.004)

TABLE 19-10. (continued)

Adjusted Analysis for Functional Stimulation Test Variables by Group

Variable	Statistic	Group		p-Value	Covariate Remarks
		Ranch Hand	Comparison		
NKCI 50/1	n	371	472		GRP*RACE (p=0.003)
Percent	Adj. Mean	****	****	****	BATCH (p<0.001)
Release	95% C.I.	****	****		DAY(BATCH) (p<0.001)
					RACE*CSMOK (p=0.013)
					OCC*PACKYR (p=0.020)
					CSMOK*PACKYR (p=0.003)

[a]Transformed from natural logarithm scale.

**Group-by-covariate interaction (0.01<p<0.05)—adjusted mean, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

****Group-by-covariate interaction (p<0.01)—Adjusted mean, confidence interval, and p-value not presented.

Unstimulated PHA Response

For the unstimulated PHA response, the unadjusted group contrast was essentially based on a two-factor model (containing group, day, and the group-by-day interaction) assuming repeated measures across days. For the unadjusted analysis, the model was expanded to include the batch-to-batch and blood draw day-to-day covariates. The Ranch Hand and Comparison contrast was not significant ($p=0.840$).

Significant or borderline significant associations with the unstimulated PHA responses were noted for the following covariates: age ($p=0.002$ for day 1 responses and $p<0.001$ for day 2 responses), race ($p=0.007$ for day 1 responses and $p<0.001$ for day 2 responses), occupation ($p=0.002$ for day 1 responses and $p=0.003$ for day 2 responses), current alcohol use ($p=0.018$ for day 2 responses), and lifetime alcohol history ($p=0.079$ for day 2 responses). For both day 1 and day 2, average unstimulated PHA responses decreased with increasing participant age. For younger participants, born in or after 1942, the average unstimulated PHA responses were 2,043 cpm and 2,224 cpm for day 1 and day 2, respectively. For those individuals born between 1923 and 1941, the average unstimulated PHA responses were 1,844 cpm and 1,918 cpm for day 1 and day 2, respectively. For the oldest group of participants, born in 1922 or before, the average unstimulated PHA responses were 1,629 cpm and 1,604 cpm for day 1 and day 2, respectively.

For race, the average unstimulated PHA response for day 1 among Blacks was 2,308 cpm and 1,902 cpm among nonblacks. For the day 2 responses, Blacks had an average of 2,749 cpm and nonblacks had an average of 2,001 cpm.

The average unstimulated PHA response was highest for the enlisted groundcrew (2,050 cpm and 2,184 cpm for day 1 and day 2, respectively); followed by the enlisted flyers (1,851 cpm and 1,955 cpm for day 1 and day 2, respectively); and officers (1,809 cpm and 1,904 cpm for day 1 and day 2, respectively).

The average unstimulated PHA response for day 2 was highest for participants with current alcohol use values of more than four drinks per day (2,375 cpm), followed by those participants having zero to one drink per day (2,057 cpm), and those with more than one but not over four drinks per day (1,843 cpm). For lifetime alcohol history, the average unstimulated PHA response for day 2 was 2,247 cpm for nondrinkers. For those participants with average lifetime alcohol values not exceeding 40 drink-years, the average unstimulated PHA response for day 2 was 1,977 cpm. For those participants with a lifetime alcohol history value over 40 drink-years, the average unstimulated PHA response for day 2 was 2,105 cpm.

For the repeated measures adjusted analysis of the unstimulated PHA responses for day 1 and day 2, the group contrast of Ranch Hand and Comparison was not significant ($p=0.933$) following adjustment for covariates. The adjusted model had the following significant terms: batch-to-batch variation ($p<0.001$); blood draw day-to-day variation ($p=0.021$); age ($p<0.001$); race ($p=0.001$); current alcohol use-by-current cigarette smoking ($p=0.007$); and current alcohol use-by-lifetime alcohol history ($p=0.039$).

PHA Net Response for Day 1 at Concentration Level 1

Ranch Hands and Comparisons did not differ significantly on the unadjusted analysis of the PHA net response for day 1 at concentration level 1 ($p=0.915$). The group contrast for this PHA net response variable was performed without adjusting for covariates, except batch-to-batch and blood draw day-to-day variation.

Significant associations were found for the PHA net responses for day 1 at concentration level 1 with age ($p<0.001$) and race ($p=0.014$). Average PHA net responses decreased with increasing age. For younger participants born in or after 1942, the average PHA net response was 111,953 cpm. Participants born between 1923 and 1941 had an average PHA net response of 91,675 cpm, and those born in or before 1922 had an average net response of 86,669 cpm. Blacks had a higher average PHA net response than nonblacks (116,774 cpm vs. 99,550 cpm, respectively).

For the adjusted analysis of the PHA net response for day 1 at concentration level 1, there was a significant group-by-current alcohol use interaction ($p=0.042$). In addition, the following covariates were significant in the adjusted model: batch-to-batch variation ($p<0.001$), blood draw day-to-day variation ($p<0.001$), age ($p<0.001$), race ($p=0.008$), and occupation ($p=0.012$). As a result of the group-by-current alcohol use interaction, Table P-3 presents group contrasts performed and significance levels within each of the following current alcohol use strata: at most one drink per day ($p=0.305$), over one but not more than four drinks per day ($p=0.489$), and over four drinks per day ($p=0.024$). Comparisons having over four drinks per day had a significantly higher adjusted mean PHA net response for day 1 at concentration level 1 than Ranch Hands also having over four drinks per day (114,309 cpm vs. 73,793 cpm). Without the group-by-current alcohol use interaction in the model, there was no significant difference between the Ranch Hands and Comparisons ($p=0.817$).

PHA Net Response for Day 1 at Concentration Level 2

The unadjusted PHA net response for day 1 at concentration level 2 was not significantly different between Ranch Hands and Comparisons ($p=0.976$). This group contrast analysis accounted for only the batch-to-batch and blood draw day-to-day covariates.

The following covariates displayed significant relationships with PHA net responses for day 1 at concentration level 2: age ($p<0.001$), race ($p=0.035$), and occupation ($p=0.012$). The average PHA net responses were inversely related with age. For participants born in or after 1942, the PHA net response was 177,443 cpm; followed by those born between 1923 and 1941, having an average of 149,059 cpm; and those born in or before 1922, with an average of 129,819 cpm. Blacks had a higher average PHA net response than nonblacks (177,087 cpm vs. 159,905 cpm). Among the enlisted groundcrew, the average PHA net response for day 1 at concentration level 2 was 166,943 cpm. The average PHA net response for enlisted flyers was lower at 158,066 cpm. Officers had the lowest average PHA net response at 154,669 for day 1 at concentration level 2.

The Ranch Hand and Comparison groups did not differ on the adjusted analysis of the PHA net responses for day 1 at concentration level 2 ($p=0.540$). For this adjusted analysis, the following significant covariates were found: batch-to-batch variation ($p<0.001$), blood draw day-to-day variation ($p<0.001$), and current cigarette smoking ($p=0.044$). This adjusted model also contained a significant age-by-race interaction ($p=0.044$).

PHA Net Response for Day 1 at Concentration Level 3

Ranch Hands and Comparisons did not differ significantly on the PHA net response for day 1 at concentration level 3 ($p=0.538$). The unadjusted analysis used only the batch-to-batch and blood draw day-to-day covariates.

As for day 1 of concentration level 2, the covariates of age, race, and occupation exhibited significant relationships with the PHA net responses for day 1 at concentration level 3 ($p<0.001$, $p=0.005$, and $p=0.002$, respectively). Lifetime cigarette smoking history displayed a borderline significant association ($p=0.055$). For younger participants, born in or after 1942, the average PHA net response for day 1 at concentration level 3 was 162,016 cpm. Participants born between 1923 and 1941 had an average PHA net response of 135,851 cpm. Individuals born in or before 1922 had an average PHA net response of 110,263 cpm. Blacks had a higher PHA net response for day 1 at concentration level 3 than did nonblacks (166,867 cpm vs. 145,282 cpm). The average PHA net responses for enlisted groundcrew, enlisted flyers, and officers were 152,947 cpm, 145,781 cpm, and 138,662 cpm, respectively. With respect to the borderline significance of the covariate lifetime cigarette smoking history, participants with lifetime smoking values greater than 0 pack-years and less than or equal to 10 pack-years had the highest PHA net response at 153,032 cpm. Participants with a lifetime cigarette smoking history value over 10 pack-years had an average of 143,911 cpm, and nonsmokers had an average of 143,768 cpm.

For the adjusted analysis of the PHA net responses for day 1 at concentration level 3, there was no group difference ($p=0.185$). The model had the following significant covariates and covariate interactions: batch-to-batch variation ($p<0.001$), blood draw day-to-day variation ($p<0.001$), age-by-race ($p=0.048$), age-by-current alcohol use ($p=0.035$), and lifetime cigarette smoking history-by-race ($p=0.043$).

PHA Net Response for Day 2 at Concentration Level 1

Ranch Hands and Comparisons did not differ significantly on unadjusted analyses of the PHA net responses for day 2 at concentration level 1 ($p=0.337$). This group contrast was based only on the batch-to-batch and blood draw day-to-day covariates.

The covariates age ($p=0.040$), occupation ($p=0.046$), and current cigarette smoking ($p=0.019$) displayed significant relationships on the PHA net responses for day 2 at concentration level 1. For participants born in or after 1942, the average PHA net response was 165,370 cpm. For individuals born between 1923 and 1941, the average PHA net response was 159,549 cpm. The average PHA net response for those born in or before 1922 was 144,773 cpm. For day 2 at

concentration level 1, officers had the highest average net response at 165,673 cpm. The next highest average net response was 161,299 cpm for the enlisted groundcrew. Enlisted flyers had an average PHA net response of 153,648 cpm. For current cigarette smoking, former smokers had the highest average PHA net response at 166,067 cpm. Those individuals who never smoked had the next highest average at 163,835 cpm. Individuals who smoked at most 20 cigarettes per day had an average PHA net response of 152,397 cpm. Participants smoking over 20 cigarettes per day had an average PHA net response of 156,143 cpm.

For the adjusted group contrast of the PHA net responses for day 2 at concentration level 1, there was no significant group difference ($p=0.474$). The adjusted model had the following significant covariates and covariate interaction: batch-to-batch variation ($p<0.001$), blood draw day-to-day variation ($p<0.001$), age ($p<0.001$), occupation ($p=0.004$), and current cigarette smoking-by-race ($p=0.015$).

PHA Net Response for Day 2 at Concentration Level 2

The unadjusted Ranch Hand and Comparison group contrast was not significant for the PHA net response for day 2 at concentration level 2 ($p=0.511$). This analysis used only the batch-to-batch and blood draw day-to-day covariates.

Age exhibited a significant covariate association with the PHA net responses for day 2 at concentration level 2 ($p<0.001$). Occupation was a borderline significant covariate ($p=0.055$). Participants born in or after 1942 had an average PHA net response of 190,416 cpm. Participants born between 1923 and 1941 had an average PHA net value of 174,418 cpm, and those born in or before 1922 had an average of 152,011 cpm. The average PHA net responses were 184,678 cpm for enlisted groundcrew, 180,597 cpm for enlisted flyers, and 175,499 cpm for officers.

The adjusted analysis of the PHA net responses for day 2 at concentration level 2 was not significantly different between the Ranch Hand and Comparison groups ($p=0.820$). The adjusted model had significant batch-to-batch and blood draw day-to-day covariates ($p<0.001$ and $p<0.001$, respectively), and a significant covariate interaction of age-by-lifetime cigarette smoking history ($p=0.027$).

PHA Net Response for Day 2 at Concentration Level 3

Ranch Hands and Comparisons did not differ significantly for the unadjusted PHA net response for day 2 at concentration level 3 ($p=0.886$). The unadjusted analysis used the batch-to-batch and blood draw day-to-day covariates.

Age ($p<0.001$), race ($p=0.005$), and occupation ($p=0.023$) were significant covariates with the PHA net responses for day 2 at concentration level 3. Participants born in or after 1942 had an average PHA net response of 134,016 cpm. For those individuals born between 1923 and 1941, the average PHA net response was 123,717 cpm. Individuals born in or before 1922 had an

average PHA net response of 100,378 cpm. The average PHA net response for Blacks was 146,588 cpm versus 126,291 cpm for nonblacks. The average PHA net responses for enlisted flyers, enlisted groundcrew, and officers were 131,229 cpm, 130,709 cpm, and 121,213 cpm, respectively.

For the PHA net responses on day 2 at concentration level 3, the adjusted group contrast of Ranch Hands and Comparisons was not significant ($p=0.683$). The adjusted model contained the following significant covariate terms: batch-to-batch variation ($p<0.001$), blood draw day-to-day variation ($p<0.001$), age ($p<0.001$), and race ($p=0.009$).

Overall PHA Net Response

For the unadjusted analysis of the six PHA net responses (for 2 harvest days at each of three concentration levels), a three-factor repeated measures model (containing group, day, concentration level, associated two-factor interactions, and a three-factor interaction) was used to evaluate the Ranch Hand and Comparison group contrast. In the context of this model, the repeated measures factors were the day and concentration level effects. The unadjusted model also included terms for batch-to-batch variation and blood draw day-to-day variation. The group contrast was not significant ($p=0.841$).

The six PHA net responses were also analyzed using covariate adjustment within the framework of the three-factor repeated measures analysis described above. The adjusted group contrast was not significant ($p=0.720$). The model had the following significant terms: batch-to-batch variation ($p<0.001$), blood draw day-to-day variation ($p<0.001$), race ($p=0.014$), and age-by-current alcohol use interaction ($p=0.035$).

Maximum of Day and Concentration Level PHA Net Response

In the unadjusted analysis of the maximum PHA net response (maximum net response of the six PHA responses), the Ranch Hand and Comparison group contrast was not significant ($p=0.506$). The batch-to-batch and blood draw day-to-day covariates were used in the analysis.

As in other PHA analyses, significant covariate associations were found for age and occupation ($p<0.001$ and $p=0.008$, respectively). The mean maximum response decreased with age (220,904 cpm for those born in or after 1942, 196,253 cpm for those born between 1923 and 1941, and 163,872 cpm for those born in or before 1922). The enlisted groundcrew had the highest mean maximum PHA net response (212,528 cpm), followed by the officers (199,887 cpm) and the enlisted flyers (198,386 cpm).

For the adjusted analysis of maximum PHA net response, there was no significant difference between the Ranch Hands and the Comparisons ($p=0.914$). Age ($p<0.001$), current cigarette smoking ($p=0.006$), batch-to-batch variation ($p<0.001$), and blood draw day-to-day variation ($p<0.001$) were significant covariates in the model.

Unstimulated MLC Response

The unadjusted Ranch Hand and Comparison group contrast was not significant for the unstimulated MLC response ($p=0.221$). The analysis included only the batch-to-batch and blood draw day-to-day covariates.

Age ($p<0.001$), race ($p<0.001$), and occupation ($p=0.002$) displayed significant associations with the unstimulated MLC responses. Participants born in or after 1942 had an unstimulated MLC average response of 4,647 cpm. Individuals born between 1923 and 1941 had an average unstimulated MLC response of 3,516 cpm. Those participants born in or before 1922 had an average unstimulated response of 2,541 cpm. Black participants had a significantly higher unstimulated MLC response than nonblack participants (6,246 cpm vs. 3,831 cpm). For enlisted groundcrew, the average unstimulated MLC response was 4,359 cpm. Officers and enlisted flyers had average unstimulated MLC responses of 3,635 cpm and 3,573 cpm, respectively.

For the adjusted analysis of the unstimulated MLC response, Ranch Hands and Comparisons did not differ significantly ($p=0.116$). For this adjusted analysis, batch-to-batch variation, blood draw day-to-day variation, and race were significant covariates ($p<0.001$, $p=0.027$, and $p<0.001$, respectively). Also, the age-by-lifetime alcohol history interaction was significant ($p=0.014$).

MLC Net Response

The unadjusted group contrast of Ranch Hands and Comparisons was not significant for the MLC net response ($p=0.647$). The analysis included only the batch-to-batch and blood draw day-to-day covariates.

Current cigarette smoking ($p<0.001$) and lifetime cigarette smoking history ($p=0.012$) displayed significant covariate relationships with the MLC net responses. Age exhibited a borderline significant association ($p=0.063$) with the MLC net responses. For the current cigarette smoking covariate, participants who never smoked and who were former smokers had average MLC net responses of 81,169 cpm and 84,935 cpm, respectively. For those individuals smoking no more than 20 cigarettes per day and those smoking more than 20 cigarettes per day, the average MLC net responses were 91,349 cpm and 99,745 cpm, respectively. For individuals with a lifetime cigarette smoking history above 10 pack-years, the average MLC net response was 91,447 cpm. For those with lifetime cigarette smoking history values between 0 and 10 pack-years, the average MLC net response was 86,642 cpm. Nonsmokers had an average MLC net response of 81,368 cpm. Participants born in or after 1942 had an average MLC net response of 90,828 cpm. Individuals born between 1923 and 1941 had an average MLC net response of 84,924 cpm, and those born in or before 1922 had an average MLC net response of 78,324 cpm.

For the adjusted analysis of the MLC net response, there was a significant group-by-race interaction ($p=0.039$). In addition, the following covariates and interactions were significant in the adjusted model: batch-to-batch variation ($p<0.001$), blood draw day-to-day variation ($p<0.001$), age ($p=0.014$), occupation ($p=0.014$), and current cigarette smoking-by-lifetime cigarette smoking history ($p=0.032$). Because of the group-by-race interaction, Ranch Hand and Comparison group contrasts were performed separately

for Blacks and nonblacks. For the Blacks, Ranch Hands had a lower adjusted mean MLC net response than the Comparisons (87,383 cpm vs. 109,376 cpm), and this group contrast was borderline significant (p=0.059). For the nonblacks, the group contrast was not significant (p=0.341). The adjusted means for nonblack Ranch Hands and nonblack Comparisons were 87,867 cpm and 85,200 cpm, respectively. Without the group-by-race interaction in the model, there was no significant difference between the Ranch Hands and Comparisons (p=0.617).

NKCA 50/1 Net Response

The unadjusted group contrast of the NKCA 50/1 net response was not significant (p=0.435). The analysis included only the batch-to-batch and blood draw day-to-day covariates.

For the NKCA 50/1 net response, significant covariate associations were displayed for the following: occupation (p=0.032), current cigarette smoking history (p=0.007), current alcohol use (p=0.006), and lifetime alcohol history (p=0.048). Officers had the highest average net response at 439.1 cpm. Enlisted flyers and enlisted groundcrew had average net responses of 405.0 cpm and 401.4 cpm, respectively. For the covariate current cigarette smoking, participants who never smoked or those who quit had average net responses of 436.4 cpm and 429.7 cpm, respectively. Smokers above 20 cigarettes per day had an average net response of 384.6 cpm, and those not exceeding 20 cigarettes per day had an average net response of 382.3 cpm. For participants with current alcohol use of more than four drinks per day, the average net response was 506.1 cpm. Individuals consuming more than one drink per day but no more than four drinks per day had an average net response of 443.9 cpm. For those individuals having at most one drink per day, the average was 408.1 cpm. Among participants with lifetime alcohol history scores above 40 drink-years, the average net response was 445.8 cpm. Participants with a lifetime alcohol history value of more than 0 drink-years but not exceeding 40 drink-years had an average net response of 412.8 cpm. Individuals with a lifetime alcohol history of 0 drink-years had an average net response of 388.9 cpm.

For the adjusted analysis of the NKCA 50/1 net response, the group-by-race interaction was significant (p=0.040). The batch-to-batch and blood draw day-to-day covariates were significant in the adjusted model (p<0.001 for both covariates). The following covariate interactions were also significant for this analysis: current cigarette smoking-by-race (p=0.014), lifetime cigarette smoking history-by-occupation (p=0.004), current cigarette smoking-by-lifetime cigarette smoking history (p=0.041), and age-by-current alcohol use (p=0.031). To examine the group-by-race interaction, Ranch Hands and Comparisons were compared for Blacks and nonblacks separately. The group contrast for the nonblacks was not significant (p=0.268) and the group contrast for the Blacks was borderline significant (p=0.065), with the Black Ranch Hands having a higher adjusted mean net response (467.1 cpm) than the Black Comparisons (359.3 cpm). Without the group-by-race interaction, the adjusted group contrast was not significant (p=0.494).

NKCA 50/1 Percent Release

No significant unadjusted group difference was found for the NKCA 50/1 percent release (p=0.569). The analysis included only the batch-to-batch and blood draw day-to-day covariates.

For the NKCA 50/1 percent release, occupation (p=0.039), current cigarette smoking (p=0.007), and current alcohol use (p=0.022) displayed significant associations. Officers had the highest average percent release at 37.3. Enlisted flyers and enlisted groundcrew had average percent releases of 34.4. For participants who never smoked or were former smokers, the average percent releases were 37.0 and 36.7, respectively. For smokers not exceeding 20 cigarettes per day, the average percent release was 32.5, and for those smoking more than 20 cigarettes per day the average percent release was 33.1. Participants with current alcohol use over four drinks per day had an average percent release of 41.8; those above one drink per day but not exceeding four drinks per day had an average percent release of 37.4; and those individuals not exceeding one drink per day had an average percent release of 34.9.

The adjusted analysis contained a significant group-by-race interaction (p=0.022). The batch-to-batch and blood draw day-to-day covariates were significant in the adjusted model (p<0.001 for both covariates). In addition, the following three covariate interactions were significant: current cigarette smoking-by-race (p=0.006), lifetime cigarette smoking history-by-occupation (p=0.020), and age-by-current alcohol use (p=0.034). Because of the group-by-race interaction, Ranch Hands and Comparisons were contrasted for Blacks and nonblacks separately. For the nonblacks, Ranch Hands and Comparisons were not significantly different (p=0.392) on their adjusted mean percent release. The Black Ranch Hands had a significantly higher average percent release than the Black Comparisons (p=0.031, 40.4% vs. 30.1%). Deleting the group-by-race interaction from the adjusted model resulted in a nonsignificant group contrast (p=0.710).

NKCI 50/1 Net Response

The unadjusted group contrast of the NKCI 50/1 net response variable was not significant (p=0.462). The analysis included only the batch-to-batch and blood draw day-to-day covariates.

Current cigarette smoking (p<0.001) and lifetime cigarette smoking history (p=0.034) exhibited significant covariate associations with the 50/1 net responses for the NKCI. Occupation also displayed a marginal association with these net responses (p=0.077). For enlisted flyers and officers, the NKCI average net responses were 822.7 cpm and 816.3 cpm, respectively. Enlisted groundcrew had an average net response of 801.2 cpm for the NKCI. For those participants who never smoked or were former smokers, the average net responses were 827.7 cpm and 817.4 cpm, respectively. Individuals who smoked no more than 20 cigarettes per day had an average net response of 787.0 cpm, and those who smoked over 20 cigarettes per day had an average net response of 789.9 cpm. For the covariate of lifetime cigarette smoking history, those participants who never smoked had the highest average net response at 827.0 cpm. Smokers with lifetime cigarette smoking history not exceeding 10 pack-years versus those above 10 pack-years had average net responses of 806.3 cpm and 802.7 cpm, respectively.

For the adjusted analysis of the NKCI 50/1 net response, there was a significant group-by-race interaction (p=0.003). This model also had the following significant covariates and interactions: batch-to-batch variation (p<0.001), blood draw day-to-day variation (p<0.001), current cigarette smoking-by-race (p=0.020), lifetime cigarette smoking history-by-occupation (p=0.031), and current cigarette smoking-by-lifetime cigarette smoking history (p=0.004). Because of the significant group-by-race interactions, group contrasts were performed separately for Blacks and nonblacks. Black Ranch Hands had a significantly higher adjusted mean net response for the NKCI than did the Black Comparisons (828.6 cpm vs. 734.7 cpm, p=0.007). The nonblack Ranch Hands and Comparisons were not significantly different (p=0.146).

NKCI 50/1 Percent Release

No significant unadjusted group difference was found for the NKCI 50/1 percent release (p=0.270). The analysis included only the batch-to-batch and blood draw day-to-day covariates.

For the NKCI 50/1 percent release, current cigarette smoking and lifetime cigarette smoking history exhibited significant covariate relationships (p<0.001 and p=0.019, respectively). For the first covariate, participants who never smoked or were former smokers had average percent releases of 68.2 and 67.3, respectively. Smokers, categorized as those with current cigarette smoking levels not exceeding 20 cigarettes per day and those exceeding 20 cigarettes per day, had the same average percent release of 65.0. For lifetime cigarette smoking history, nonsmokers had an average percent release of 68.2. For those participants between 0 and 10 pack-years, the average percent release was 66.6. Those participants with more than 10 pack-years of lifetime cigarette smoking history had an average percent release of 66.0.

For the adjusted analysis of the NKCI 50/1 percent release, the group-by-race interaction was significant (p=0.003). In addition, this adjusted model had the following significant covariates and interactions: batch-to-batch variation (p<0.001), blood draw day-to-day variation (p<0.001), current cigarette smoking-by-race (p=0.013), lifetime cigarette smoking history-by-occupation (p=0.020), and current cigarette smoking-by-lifetime cigarette smoking history (p=0.003). To investigate the group-by-race interaction, Ranch Hands and Comparisons were compared separately for Blacks and nonblacks. For the NKCI, the Black Ranch Hands had a significantly higher adjusted mean percent release than the Black Comparisons (67.9% vs. 60.5%, p=0.008). For the nonblacks, the Ranch Hands had a lower adjusted mean percent release that was marginally different from that of the Comparisons (66.5% vs. 67.7%, p=0.069).

Exposure Index Analysis

The unadjusted and adjusted results of the exposure index analyses of the Ranch Hands are presented by occupation in Tables 19-11 and 19-12, respectively. The adjusted models investigated effects of the covariates of race, age, current cigarette smoking, lifetime cigarette smoking history, current alcohol use, and lifetime alcohol history; and the exposure index-by-covariate interactions. An overall summary of the significant exposure index-by-covariate interactions is provided in Table 19-13. For these interactions, detailed results are presented by strata in Table P-4 of Appendix P.

TABLE 19-11.

Unadjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Exposure Index Medium	Exposure Index High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
Composite Skin Test Diagnosis	Officer	n	93	96	102	Overall		0.090
		Number/%						
		Abnormal	8 8.6%	4 4.2%	2 2.0%	M vs. L	0.46 (0.13,1.59)	0.342
		Normal	85 91.4%	92 95.8%	100 98.0%	H vs. L	0.21 (0.04,1.03)	0.073
	Enlisted Flyer	n	40	44	40	Overall		0.100
		Number/%						
		Abnormal	6 15.0%	1 2.3%	3 7.5%	M vs. L	0.13 (0.02,1.15)	0.083
		Normal	34 85.0%	43 97.7%	37 92.5%	H vs. L	0.46 (0.11,1.98)	0.482
	Enlisted Groundcrew	n	118	105	110	Overall		0.127
		Number/%						
		Abnormal	6 5.1%	13 12.4%	8 7.3%	M vs. L	2.64 (0.97,7.21)	0.087
		Normal	112 94.9%	92 87.6%	102 92.7%	H vs. L	1.46 (0.49,4.36)	0.680
CD2 Cells	Officer	n	51	53	48	Overall		0.518
		Mean[a]	1,489.1	1,606.3	1,574.4	M vs. L	—	0.254
		95% C.I.[a]	(1,344.1, 1,649.8)	(1,482.7, 1,740.2)	(1,419.0, 1,746.8)	H vs. L	—	0.457
	Enlisted Flyer	n	20	24	24	Overall		0.597
		Mean[a]	1,656.2	1,569.2	1,722.1	M vs. L	—	0.589
		95% C.I.[a]	(1,414.7, 1,938.8)	(1,392.9, 1,767.7)	(1,528.9, 1,939.7)	H vs. L	—	0.695
	Enlisted Groundcrew	n	43	64	47	Overall		0.733
		Mean[a]	1,701.5	1,693.2	1,615.1	M vs. L	—	0.941
		95% C.I.[a]	(1,550.4, 1,867.3)	(1,554.7 1,844.1)	(1,437.4, 1,814.6)	H vs. L	—	0.500

TABLE 19-11. (continued)

Unadjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
CD4 Cells	Officer	n	51	53	48	Overall		0.311
		Mean[a]	823.2	932.3	842.7	M vs. L	—	0.100
		95% C.I.[a]	(735.9, 920.9)	(847.2, 1,025.9)	(722.8, 982.5)	H vs. L	—	0.808
	Enlisted Flyer	n	20	24	25	Overall		0.852
		Mean[a]	971.9	914.7	950.9	M vs. L	—	0.610
		95% C.I.[a]	(794.8, 1,188.4)	(817.2, 1,023.9)	(831.0, 1,088.0)	H vs. L	—	0.856
	Enlisted Groundcrew	n	43	63	47	Overall		0.550
		Mean[a]	974.7	977.6	907.2	M vs. L	—	0.966
		95% C.I.[a]	(883.6, 1,075.3)	(895.0, 1,067.8)	(796.3, 1,033.5)	H vs. L	—	0.391
CD8 Cells	Officer	n	51	53	47	Overall		0.817
		Mean[a]	461.7	452.6	480.3	M vs. L	—	0.831
		95% C.I.[a]	(401.7, 530.7)	(401.3, 510.4)	(421.3, 547.6)	H vs. L	—	0.689
	Enlisted Flyer	n	20	24	25	Overall		0.398
		Mean[a]	438.9	465.7	527.0	M vs. L	—	0.680
		95% C.I.[a]	(350.1, 550.2)	(392.0, 553.2)	(442.2, 628.1)	H vs. L	—	0.210
	Enlisted Groundcrew	n	43	64	46	Overall		0.971
		Mean[a]	500.9	489.4	494.8	M vs. L	—	0.805
		95% C.I.[a]	(430.2, 583.3)	(438.4, 546.4)	(427.7, 572.4)	H vs. L	—	0.909

TABLE 19-11. (continued)

Unadjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
			Low	Medium	High			
CD20 Cells	Officer	n	51	53	48	Overall		0.939
		Mean[a]	142.8	146.0	140.4	M vs. L	—	0.848
		95% C.I.[a]	(124.6, 163.6)	(122.7, 173.7)	(122.6, 160.8)	H vs. L	—	0.864
	Enlisted Flyer	n	20	24	25	Overall		0.388
		Mean[a]	176.2	148.0	142.0	M vs. L	—	0.300
		95% C.I.[a]	(135.1, 229.8)	(121.2, 180.7)	(115.4, 174.7)	H vs. L	—	0.209
	Enlisted Groundcrew	n	43	64	47	Overall		0.825
		Mean[a]	173.5	161.5	167.1	M vs. L	—	0.540
		95% C.I.[a]	(147.5, 204.1)	(138.7, 188.1)	(141.6, 197.1)	H vs. L	—	0.750
CD14 Cells	Officer	n	51	54	48	Overall		0.692
		Mean[a]	31.9	31.3	35.1	M vs. L	—	0.889
		95% C.I.[a]	(26.5,38.4)	(25.9,37.9)	(28.6,43.1)	H vs. L	—	0.505
	Enlisted Flyer	n	20	24	25	Overall		0.078
		Mean[a]	39.4	29.8	22.9	M vs. L	—	0.241
		95% C.I.[a]	(28.4,54.8)	(21.7,41.0)	(16.7,31.4)	H vs. L	—	0.025
	Enlisted Groundcrew	n	43	64	48	Overall		0.897
		Mean[a]	31.4	29.8	31.5	M vs. L	—	0.714
		95% C.I.[a]	(25.8,38.3)	(24.7,36.0)	(26.1,37.9)	H vs. L	—	0.987

TABLE 19-11. (continued)

Unadjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Exposure Index Medium	Exposure Index High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
CD25 Cells[b]	Officer	n	39	37	30	Overall		0.579
		Mean[a]	10.9	11.0	14.0	M vs. L	—	0.975
		95% C.I.[a]	(8.0,14.9)	(7.9,15.3)	(9.1,21.6)	H vs. L	—	0.359
		n	51	54	48	Overall		0.318
		Number/%						
		0	12 23.5%	17 31.5%	18 37.5%	M vs. L	—	0.490
		>0	39 76.5%	37 68.5%	30 62.5%	H vs. L	—	0.196
	Enlisted Flyer	n	13	15	18	Overall		0.360
		Mean[a]	13.3	9.2	8.3	M vs. L	—	0.308
		95% C.I.[a]	(8.8,20.2)	(5.4,15.8)	(5.6,12.5)	H vs. L	—	0.134
		n	20	24	25	Overall		0.766
		Number/%						
		0	7 35.0%	9 37.5%	7 28.0%	M vs. L	—	0.999
		>0	13 65.0%	15 62.5%	18 72.0%	H vs. L	—	0.854
	Enlisted Groundcrew	n	31	48	37	Overall		0.283
		Mean[a]	13.8	11.1	9.3	M vs. L	—	0.356
		95% C.I.[a]	(10.0,19.0)	(8.1,15.1)	(6.7,12.8)	H vs. L	—	0.095
		n	43	64	47	Overall		0.764
		Number/%						
		0	12 27.9%	16 25.0%	10 21.3%	M vs. L	—	0.906
		>0	31 72.1%	48 75.0%	37 78.7%	H vs. L	—	0.626

TABLE 19-11. (continued)

Unadjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Exposure Index Medium	Exposure Index High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
HLA-DR Cells	Officer	n	51	54	48	Overall		0.748
		Mean[a]	401.0	420.7	427.6	M vs. L	—	0.584
		95% C.I.[a]	(362.4, 443.7)	(366.4, 483.1)	(380.8, 480.1)	H vs. L	—	0.413
	Enlisted Flyer	n	20	24	25	Overall		0.137
		Mean[a]	504.1	416.1	389.0	M vs. L	—	0.133
		95% C.I.[a]	(414.1, 613.7)	(357.0, 484.9)	(322.9, 468.6)	H vs. L	—	0.069
	Enlisted Groundcrew	n	43	64	48	Overall		0.760
		Mean[a]	465.7	439.5	447.8	M vs. L	—	0.462
		95% C.I.[a]	(417.6, 519.4)	(396.7, 487.0)	(400.1, 501.1)	H vs. L	—	0.626
CD4/CD8 Ratio	Officer	n	51	53	47	Overall		0.251
		Mean[a]	1.78	2.06	1.82	M vs. L	—	0.152
		95% C.I.[a]	(1.54,2.06)	(1.81,2.35)	(1.63,2.04)	H vs. L	—	0.825
	Enlisted Flyer	n	20	24	25	Overall		0.248
		Mean[a]	2.21	1.96	1.80	M vs. L	—	0.304
		95% C.I.[a]	(1.83,2.68)	(1.72,2.24)	(1.52,2.15)	H vs. L	—	0.128
	Enlisted Groundcrew	n	43	63	46	Overall		0.425
		Mean[a]	1.95	2.01	1.81	M vs. L	—	0.684
		95% C.I.[a]	(1.69,2.24)	(1.83,2.21)	(1.61,2.04)	H vs. L	—	0.446

TABLE 19-11. (continued)

Unadjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
TLC	Officer	n	51	54	48	Overall		0.551
		Mean[a]	1,845.6	1,972.6	1,922.9	M vs. L	—	0.279
		95% C.I.[a]	(1,686.0, 2,020.3)	(1,821.7, 2,135.4)	(1,750.5, 2,112.3)	H vs. L	—	0.516
	Enlisted Flyer	n	20	24	25	Overall		0.544
		Mean[a]	2,179.9	1,978.5	2,087.0	M vs. L	—	0.275
		95% C.I.[a]	(1,867.9, 2,544.0)	(1,766.6, 2,215.9)	(1,885.8, 2,309.8)	H vs. L	—	0.620
	Enlisted Groundcrew	n	43	64	48	Overall		0.681
		Mean[a]	2,099.4	2,112.4	2,003.1	M vs. L	—	0.925
		95% C.I.[a]	(1,925.7, 2,288.7)	(1,951.5, 2,286.6)	(1,788.3, 2,243.8)	H vs. L	—	0.504
IgG	Officer	n	125	119	118	Overall		0.973
		Mean	1,006.7	1,010.3	1,013.3	M vs. L	—	0.898
		95% C.I.	(970.5, 1,042.8)	(971.5, 1,049.2)	(966.6, 1,060.0)	H vs. L	—	0.816
	Enlisted Flyer	n	53	62	53	Overall		0.420
		Mean	1,038.6	1,016.8	979.8	M vs. L	—	0.615
		95% C.I.	(974.9, 1,102.4)	(959.0, 1,074.5	(914.6, 1,045.1)	H vs. L	—	0.194
	Enlisted Groundcrew	n	145	150	138	Overall		0.973
		Mean	1,067.6	1,070.5	1,063.5	M vs. L	—	0.924
		95% C.I.	(1,027.3, 1,107.9)	(1,025.5, 1,115.4)	(1,022.3, 1,104.6)	H vs. L	—	0.890

TABLE 19-11. (continued)

Unadjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Exposure Index Medium	Exposure Index High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
IgA	Officer	n	125	119	118	Overall		0.508
		Mean[a]	207.42	199.05	193.35	M vs. L	—	0.500
		95% C.I.[a]	(191.65, 224.50)	(180.98, 218.92)	(177.39, 210.54)	H vs. L	—	0.248
	Enlisted Flyer	n	53	62	53	Overall		0.218
		Mean[a]	225.57	195.85	215.75	M vs. L	—	0.091
		95% C.I.[a]	(200.60, 253.64)	(174.65, 219.62)	(190.56, 244.27)	H vs. L	—	0.606
	Enlisted Groundcrew	n	145	150	138	Overall		0.632
		Mean[a]	206.57	216.95	212.77	M vs. L	—	0.341
		95% C.I.[a]	(192.53, 221.63)	(200.86, 234.32)	(197.85, 228.82)	H vs. L	—	0.574
IgM	Officer	n	125	119	117	Overall		0.718
		Mean[a]	108.59	113.16	113.73	M vs. L	—	0.509
		95% C.I.[a]	(100.97, 116.78)	(102.52, 124.90)	(103.48, 124.99)	H vs. L	—	0.461
	Enlisted Flyer	n	53	62	53	Overall		0.495
		Mean[a]	110.62	101.04	110.80	M vs. L	—	0.316
		95% C.I.[a]	(97.43, 125.60)	(90.31, 113.03)	(95.50, 128.55)	H vs. L	—	0.986
	Enlisted Groundcrew	n	145	150	138	Overall		0.442
		Mean[a]	109.32	116.54	111.26	M vs. L	—	0.217
		95% C.I.[a]	(101.28, 118.00)	(108.80, 124.83)	(103.03, 120.14)	H vs. L	—	0.740

TABLE 19-11. (continued)

Unadjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
Unstimulated PHA Response	Officer	n	50	53	46	Overall		0.511
		Mean[a]	1,953	1,756	1,940	M vs. L	—	0.313
		95% C.I.[a]	(1,703, 2,239)	(1,508, 2,045)	(1,683, 2,237)	H vs. L	—	0.948
	Enlisted Flyer	n	20	23	25	Overall		0.275
		Mean[a]	1,913	1,706	2,168	M vs. L	—	0.509
		95% C.I.[a]	(1,470, 2,491)	(1,375, 2,117)	(1,848, 2,544)	H vs. L	—	0.412
	Enlisted Groundcrew	n	41	63	47	Overall		0.883
		Mean[a]	2,198	2,085	2,102	M vs. L	—	0.648
		95% C.I.[a]	(1,824, 2,648)	(1,822, 2,387)	(1,834, 2,409)	H vs. L	—	0.701
PHA Net Response (day 1, conc. 1)	Officer	n	50	52	47	Overall		0.714
		Mean	96,518	103,412	95,338	M vs. L	—	0.500
		95% C.I.	(83,052, 109,984)	(88,672, 118,151)	(79,062, 111,615)	H vs. L	—	0.913
	Enlisted Flyer	n	20	24	25	Overall		0.494
		Mean	92,996	79,423	97,148	M vs. L	—	0.420
		95% C.I.	(69,412, 116,581)	(57,034, 101,812)	(76,811, 117,484)	H vs. L	—	0.794
	Enlisted Groundcrew	n	43	64	48	Overall		0.804
		Mean	98,018	97,832	104,742	M vs. L	—	0.986
		95% C.I.	(80,279, 115,757)	(85,059, 110,605)	(85,375, 124,109)	H vs. L	—	0.620

TABLE 19-11. (continued)

Unadjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Exposure Index Medium	Exposure Index High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
PHA Net Response (day 1, conc. 2)	Officer	n	50	52	47	Overall		0.439
		Mean	141,287	159,755	148,838	M vs. L	—	0.182
		95% C.I.	(123,201, 159,374)	(139,855, 179,654)	(125,933, 171,743)	H vs. L	—	0.611
	Enlisted Flyer	n	20	24	25	Overall		0.111
		Mean	173,558	136,739	171,800	M vs. L	—	0.077
		95% C.I.	(143,420, 203,696)	(110,393, 163,085)	(146,076, 197,524)	H vs. L	—	0.931
	Enlisted Groundcrew	n	43	64	48	Overall		0.955
		Mean	172,510	177,018	174,083	M vs. L	—	0.766
		95% C.I.	(149,054, 195,967)	(158,601, 195,434)	(150,550, 197,615)	H vs. L	—	0.927
PHA Net Response (day 1, conc. 3)	Officer	n	50	52	47	Overall		0.471
		Mean	127,960	143,506	136,771	M vs. L	—	0.203
		95% C.I.	(111,672, 144,248)	(126,212, 160,800)	(116,978, 156,565)	H vs. L	—	0.500
	Enlisted Flyer	n	20	24	25	Overall		0.067
		Mean	165,631	126,209	158,427	M vs. L	—	0.033
		95% C.I.	(140,307, 190,955)	(102,257, 150,161)	(134,311, 182,542)	H vs. L	—	0.691
	Enlisted Groundcrew	n	43	64	48	Overall		0.686
		Mean	166,100	165,540	155,349	M vs. L	—	0.968
		95% C.I.	(143,296, 188,903)	(149,491, 181,589)	(136,431, 174,268)	H vs. L	—	0.476

TABLE 19-11. (continued)

Unadjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
PHA Net Response (day 2, conc. 1)	Officer	n	50	54	47	Overall		0.127
		Mean	163,987	169,754	142,635	M vs. L	—	0.674
		95% C.I.	(145,159, 182,815)	(150,760, 188,749)	(123,096, 162,175)	H vs. L	—	0.126
	Enlisted Flyer	n	20	23	25	Overall		0.406
		Mean	161,962	135,314	156,092	M vs. L	—	0.262
		95% C.I.	(132,926, 190,997)	(100,776, 169,853)	(135,114, 177,071)	H vs. L	—	0.744
	Enlisted Groundcrew	n	41	63	46	Overall		0.943
		Mean	169,072	164,308	167,752	M vs. L	—	0.750
		95% C.I.	(146,217, 191,926)	(146,038, 182,578)	(146,929, 188,574)	H vs. L	—	0.933
PHA Net Response (day 2, conc. 2)	Officer	n	50	54	47	Overall		0.104
		Mean	169,516	176,020	151,107	M vs. L	—	0.596
		95% C.I.	(151,984, 187,048)	(159,598, 192,443)	(135,717, 166,496)	H vs. L	—	0.127
	Enlisted Flyer	n	20	23	25	Overall		0.369
		Mean	197,085	173,968	199,183	M vs. L	—	0.279
		95% C.I.	(169,446, 224,723)	(143,925, 204,012)	(174,547, 223,818)	H vs. L	—	0.912
	Enlisted Groundcrew	n	41	63	46	Overall		0.953
		Mean	192,394	196,800	193,698	M vs. L	—	0.772
		95% C.I.	(170,008, 214,780)	(177,728, 215,873)	(172,282, 215,113)	H vs. L	—	0.935

TABLE 19-11. (continued)

Unadjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
			Low	Medium	High			
PHA Net Response (day 2, conc. 3)	Officer	n	50	54	47	Overall		0.294
		Mean	117,323	120,887	105,378	M vs. L	—	0.732
		95% C.I.	(102,922, 131,724)	(106,533, 135,240)	(91,859, 118,897)	H vs. L	—	0.240
	Enlisted Flyer	n	20	23	25	Overall		0.549
		Mean	133,841	122,395	141,992	M vs. L	—	0.509
		95% C.I.	(116,575, 151,107)	(93,518, 151,271)	(115,630, 168,354)	H vs. L	—	0.615
	Enlisted Groundcrew	n	41	63	46	Overall		0.701
		Mean	141,118	139,131	131,379	M vs. L	—	0.870
		95% C.I.	(124,293, 157,943)	(123,531, 154,732)	(115,711, 147,046)	H vs. L	—	0.408
Overall PHA Net Response	Officer	n	49	52	46	Overall		0.433
		Mean	135,880	144,803	130,914	M vs. L	—	0.407
		95% C.I.	(121,300, 150,461)	(129,772, 159,835)	(115,205, 146,623)	H vs. L	—	0.650
	Enlisted Flyer	n	20	23	25	Overall		0.217
		Mean	154,179	129,797	154,107	M vs. L	—	0.159
		95% C.I.	(132,437, 175,920)	(105,199, 154,395)	(134,375, 173,839)	H vs. L	—	0.996
	Enlisted Groundcrew	n	41	63	46	Overall		0.998
		Mean	156,709	156,360	156,002	M vs. L	—	0.976
		95% C.I.	(137,890, 175,527)	(142,764, 169,957)	(138,963, 173,041)	H vs. L	—	0.957

TABLE 19-11. (continued)

Unadjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
Maximum PHA Net Response	Officer	n	49	52	46	Overall		0.351
		Mean	188,315	199,596	179,981	M vs. L	—	0.401
		95% C.I.	(169,815, 206,816)	(181,336, 217,856)	(158,967, 200,995)	H vs. L	—	0.547
	Enlisted Flyer	n	20	23	25	Overall		0.323
		Mean	214,337	190,274	216,475	M vs. L	—	0.231
		95% C.I.	(184,236, 244,438)	(159,944, 220,605)	(194,428, 238,522)	H vs. L	—	0.913
	Enlisted Groundcrew	n	41	63	46	Overall		0.852
		Mean	216,339	223,889	217,546	M vs. L	—	0.614
		95% C.I.	(192,781, 239,898)	(205,245, 242,534)	(195,630, 239,461)	H vs. L	—	0.940
Unstimulated MLC Response	Officer	n	49	54	47	Overall		0.352
		Mean[a]	4,187	3,960	3,330	M vs. L	—	0.731
		95% C.I.[a]	(3,394, 5,167)	(3,131, 5,009)	(2,669, 4,154)	H vs. L	—	0.144
	Enlisted Flyer	n	20	23	24	Overall		0.393
		Mean[a]	3,709	3,177	4,404	M vs. L	—	0.526
		95% C.I.[a]	(2,650, 5,192)	(2,279, 4,429)	(3,136, 6,184)	H vs. L	—	0.489
	Enlisted Groundcrew	n	43	62	48	Overall		0.834
		Mean[a]	5,001	4,549	4,566	M vs. L	—	0.555
		95% C.I.[a]	(3,900, 6,414)	(3,740, 5,533)	(3,476, 5,998)	H vs. L	—	0.633

TABLE 19-11. (continued)

Unadjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Exposure Index Medium	Exposure Index High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
MLC Net Response	Officer	n	49	54	47	Overall		0.977
		Mean	91,587	90,282	89,528	M vs. L	—	0.898
		95% C.I.	(77,545, 105,629)	(76,340, 104,225)	(78,400, 100,656)	H vs. L	—	0.823
	Enlisted Flyer	n	20	23	24	Overall		0.220
		Mean	104,580	90,817	111,932	M vs. L	—	0.263
		95% C.I.	(84,185, 124,975)	(78,839, 102,795)	(93,191, 130,673)	H vs. L	—	0.606
	Enlisted Groundcrew	n	43	62	48	Overall		0.900
		Mean	96,778	92,503	94,910	M vs. L	—	0.638
		95% C.I.	(82,289, 111,266)	(81,676, 103,330)	(80,348, 109,473)	H vs. L	—	0.860
NKCA 50/1 Net Response	Officer	n	51	53	48	Overall		0.829
		Mean	470.6	444.7	450.6	M vs. L	—	0.556
		95% C.I.	(408.0, 533.2)	(385.8, 503.6)	(386.4, 514.9)	H vs. L	—	0.664
	Enlisted Flyer	n	19	24	25	Overall		0.934
		Mean	387.9	399.5	381.0	M vs. L	—	0.820
		95% C.I.	(324.1, 451.8)	(327.8, 471.2)	(304.7, 457.4)	H vs. L	—	0.897
	Enlisted Groundcrew	n	42	62	46	Overall		0.780
		Mean	398.9	410.9	426.6	M vs. L	—	0.748
		95% C.I.	(336.2, 461.6)	(368.3, 453.5)	(374.2, 478.9)	H vs. L	—	0.506

TABLE 19-11. (continued)

Unadjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
NKCA 50/1 Percent Release	Officer	n	51	53	48	Overall		0.853
		Mean	39.1	38.0	37.2	M vs. L	—	0.740
		95% C.I.	(34.3,43.9)	(33.8,42.2)	(32.7,41.8)	H vs. L	—	0.586
	Enlisted Flyer	n	19	24	25	Overall		0.819
		Mean	33.0	34.1	31.6	M vs. L	—	0.779
		95% C.I.	(27.8,38.2)	(28.8,39.4)	(25.7,37.6)	H vs. L	—	0.746
	Enlisted Groundcrew	n	42	62	46	Overall		0.859
		Mean	33.2	34.5	34.8	M vs. L	—	0.677
		95% C.I.	(28.6,37.9)	(30.8,38.1)	(31.1,38.6)	H vs. L	—	0.595
NKCI 50/1 Net Response	Officer	n	50	53	45	Overall		0.208
		Mean	809.6	838.7	888.4	M vs. L	—	0.514
		95% C.I.	(748.9, 870.4)	(776.5, 901.0)	(831.1, 945.7)	H vs. L	—	0.069
	Enlisted Flyer	n	20	24	25	Overall		0.247
		Mean	829.2	756.6	862.4	M vs. L	—	0.291
		95% C.I.	(718.6, 939.8)	(677.4, 835.8)	(775.7, 949.2)	H vs. L	—	0.641
	Enlisted Groundcrew	n	42	64	48	Overall		0.363
		Mean	867.9	802.6	846.5	M vs. L	—	0.211
		95% C.I.	(781.7, 954.1)	(749.6, 855.6)	(781.3, 911.7)	H vs. L	—	0.696

TABLE 19-11. (continued)

Unadjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Exposure Index Medium	Exposure Index High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
NKCI 50/1	Officer	n	50	53	45	Overall		0.765
Percent		Mean	69.2	68.2	67.6	M vs. L	—	0.659
Release		95% C.I.	(65.8,72.5)	(65.3,71.1)	(65.5,69.8)	H vs. L	—	0.454
	Enlisted	n	20	24	25	Overall		0.421
	Flyer	Mean	65.2	64.3	68.2	M vs. L	—	0.779
		95% C.I.	(60.8,69.6)	(59.5,69.0)	(64.0,72.5)	H vs. L	—	0.337
	Enlisted	n	42	64	48	Overall		0.798
	Groundcrew	Mean	64.5	65.3	66.1	M vs. L	—	0.746
		95% C.I.	(61.6,67.5)	(62.4,68.1)	(63.2,69.0)	H vs. L	—	0.475

—Estimated relative risk not applicable.

[a]Transformed from natural logarithm scale.

[b]CD25 cell counts contained both zero values and positive values. Exposure index categories were compared on mean of positive CD25 cell counts and on proportion of zero CD25 cell counts.

TABLE 19-12.

Adjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Composite Skin Test Diagnosis	Officer	n	92	94	102	Overall		0.131**
						M vs. L	0.52 (0.14,1.88)**	0.321**
						H vs. L	0.23 (0.05,1.13)**	0.070**
	Enlisted Flyer	n	39	43	40	Overall		0.014**
						M vs. L	—**	—**
						H vs. L	0.57 (0.12,2.70)**	0.482**
	Enlisted Groundcrew	n	115	105	108	Overall		****
						M vs. L	****	****
						H vs. L	****	****
CD2 Cells	Officer	n	51	53	48	Overall		0.559
		Adj. Mean[a]	1,446.9	1,558.1	1,521.7	M vs. L	—	0.288
		95% C.I.[a]	(1,016.3, 2,059.9)	(1,112.2, 2,182.7)	(1,071.5, 2,161.0)	H vs. L	—	0.478
	Enlisted Flyer	n	20	24	24	Overall		****
		Adj. Mean	****	****	****	M vs. L	—	****
		95% C.I.	****	****	****	H vs. L	—	****
	Enlisted Groundcrew	n	42	64	47	Overall		0.961**
		Adj. Mean**[a]	1,635.9	1,616.5	1,601.2	M vs. L	—	0.867**
		95% C.I.**[a]	(1,432.0, 1,868.9)	(1,432.9, 1,823.5)	(1,412.3, 1,815.4)	H vs. L	—	0.780**

TABLE 19-12. (continued)

Adjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
			Low	Medium	High			
CD4 Cells	Officer	n	51	53	48	Overall		0.188
		Adj. Mean[a]	686.0	789.8	694.6	M vs. L	—	0.104
		95% C.I.[a]	(442.9, 1,062.5)	(520.2, 1,199.1)	(449.9, 1,072.6)	H vs. L	—	0.887
	Enlisted Flyer	n	20	24	25	Overall		0.724**
		Adj. Mean**[a]	929.1	958.2	1,012.0	M vs. L	—	0.778**
		95% C.I.**[a]	(734.0, 1,176.2)	(758.5, 1,210.5)	(798.0, 1,283.5)	H vs. L	—	0.438**
	Enlisted Groundcrew	n	42	63	47	Overall		****
		Adj. Mean	****	****	****	M vs. L	—	****
		95% C.I.	****	****	****	H vs. L	—	****
CD8 Cells	Officer	n	51	53	47	Overall		****
		Adj. Mean	****	****	****	M vs. L	—	****
		95% C.I.	****	****	****	H vs. L	—	****
	Enlisted Flyer	n	20	24	25	Overall		****
		Adj. Mean	****	****	****	M vs. L	—	****
		95% C.I.	****	****	****	H vs. L	—	****
	Enlisted Groundcrew	n	42	64	46	Overall		****
		Adj. Mean	****	****	****	M vs. L	—	****
		95% C.I.	****	****	****	H vs. L	—	****

TABLE 19-12. (continued)

Adjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
			Low	Medium	High			
CD20 Cells	Officer	n	51	53	48	Overall		****
		Adj. Mean	****	****	****	M vs. L	—	****
		95% C.I.	****	****	****	H vs. L	—	****
	Enlisted Flyer	n	20	24	25	Overall		0.783
		Adj. Mean[a]	186.8	175.1	166.4	M vs. L	—	0.694
		95% C.I.[a]	(131.0, 266.3)	(123.2, 248.8)	(116.4, 237.9)	H vs. L	—	0.486
	Enlisted Groundcrew	n	42	64	47	Overall		****
		Adj. Mean	****	****	****	M vs. L	—	****
		95% C.I.	****	****	****	H vs. L	—	****
CD14 Cells	Officer	n	51	54	48	Overall		0.638
		Adj. Mean[a]	31.7	29.5	33.6	M vs. L	—	0.601
		95% C.I.[a]	(15.6,64.7)	(14.9,58.1)	(16.6,68.1)	H vs. L	—	0.690
	Enlisted Flyer	n	20	24	25	Overall		0.185
		Adj. Mean[a]	32.0	26.9	20.3	M vs. L	—	0.491
		95% C.I.[a]	(18.6,54.9)	(15.7,45.9)	(11.8,35.0)	H vs. L	—	0.075
	Enlisted Groundcrew	n	42	64	48	Overall		0.813**
		Adj. Mean**[a]	26.2	24.6	26.7	M vs. L	—	0.654**
		95% C.I.**[a]	(20.2,34.0)	(19.4,31.1)	(21.0,34.1)	H vs. L	—	0.891**

TABLE 19-12. (continued)

Adjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
CD25 Cells[b]	Officer	n	39	37	30	Overall		0.852**
		Adj. Mean**[a]	13.8	13.6	15.6	M vs. L	—	0.966**
		95% C.I.**[a]	(4.6,41.7)	(4.8,38.7)	(5.1,47.6)	H vs. L	—	0.630**
	Enlisted Flyer	n	13	15	18	Overall		0.702
		Adj. Mean[a]	11.1	8.8	8.2	M vs. L	—	0.547
		95% C.I.[a]	(5.1,24.2)	(3.7,20.8)	(3.8,17.8)	H vs. L	—	0.413
	Enlisted Groundcrew	n	30	48	37	Overall		0.433
		Adj. Mean[a]	12.5	10.5	8.9	M vs. L	—	0.477
		95% C.I.[a]	(7.7,20.4)	(7.0,15.8)	(5.7,14.0)	H vs. L	—	0.197
HLA-DR Cells	Officer	n	51	54	48	Overall		0.664
		Adj. Mean[a]	391.2	416.3	420.9	M vs. L	—	0.468
		95% C.I.[a]	(253.3, 604.2)	(275.0, 630.1)	(273.4, 648.1)	H vs. L	—	0.402
	Enlisted Flyer	n	20	24	25	Overall		0.511
		Adj. Mean[a]	476.3	435.1	408.7	M vs. L	—	0.491
		95% C.I.[a]	(359.0, 632.0)	(328.8, 575.9)	(307.4, 543.6)	H vs. L	—	0.249
	Enlisted Groundcrew	n	42	64	48	Overall		0.629**
		Adj. Mean**[a]	447.4	419.4	444.4	M vs. L	—	0.397**
		95% C.I.**[a]	(388.2, 515.5)	(368.9, 476.8)	(389.1, 507.6)	H vs. L	—	0.934**

TABLE 19-12. (continued)

Adjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
CD4/CD8 Ratio	Officer	n	51	53	47	Overall		****
		Adj. Mean	****	****	****	M vs. L	—	****
		95% C.I.	****	****	****	H vs. L	—	****
	Enlisted Flyer	n	20	24	25	Overall		0.211
		Adj. Mean[a]	1.98	1.76	1.58	M vs. L	—	0.369
		95% C.I.[a]	(1.50,2.60)	(1.34,2.31)	(1.20,2.08)	H vs. L	—	0.080
	Enlisted Groundcrew	n	42	63	46	Overall		0.450**
		Adj. Mean**[a]	2.08	2.14	1.92	M vs. L	—	0.754**
		95% C.I.**[a]	(1.78,2.44)	(1.84,2.48)	(1.65,2.24)	H vs. L	—	0.386**
TLC	Officer	n	51	54	48	Overall		0.534
		Adj. Mean[a]	1,844.3	1,966.0	1,931.6	M vs. L	—	0.276
		95% C.I.[a]	(1,695.8, 2,005.7)	(1,812.0, 2,133.1)	(1,771.5, 2,106.2)	H vs. L	—	0.444
	Enlisted Flyer	n	20	24	25	Overall		0.666
		Adj. Mean[a]	2,041.5	2,022.0	2,154.0	M vs. L	—	0.906
		95% C.I.[a]	(1,810.3, 2,302.2)	(1,817.8, 2,249.2)	(1,939.5, 2,392.3)	H vs. L	—	0.511
	Enlisted Groundcrew	n	43	64	48	Overall		****
		Adj. Mean[a]	****	****	****	M vs. L	—	****
		95% C.I.[a]	****	****	****	H vs. L	—	****

TABLE 19-12. (continued)

Adjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
IgG	Officer	n	125	119	118	Overall		0.032
		Adj. Mean	962.6	1,032.7	1,242.6	M vs. L	—	0.492
		95% C.I.	(804.8, 1,120.3)	(903.4, 1,162.1)	(1,034.8, 1,800.4)	H vs. L	—	0.012
	Enlisted Flyer	n	53	62	53	Overall		0.344
		Adj. Mean	1,039.0	1,020.1	975.5	M vs. L	—	0.660
		95% C.I.	(976.0, 1,102.0)	(961.8, 1,078.5)	(912.3, 1,038.6)	H vs. L	—	0.156
	Enlisted Groundcrew	n	145	150	138	Overall		****
		Adj. Mean	****	****	****	M vs. L	—	****
		95% C.I.	****	****	****	H vs. L	—	****
IgA	Officer	n	125	119	118	Overall		0.508**
		Adj. Mean**[a]	207.42	199.05	193.25	M vs. L	—	0.500**
		95% C.I.**[a]	(191.65, 224.50)	(180.98, 218.92)	(177.39, 210.54)	H vs. L	—	0.248**
	Enlisted Flyer	n	53	62	53	Overall		0.218
		Adj. Mean[a]	225.57	195.85	215.75	M vs. L	—	0.091
		95% C.I.[a]	(200.60, 253.64)	(174.65, 219.62)	(190.56, 244.27)	H vs. L	—	0.606
	Enlisted Groundcrew	n	142	150	136	Overall		0.423**
		Adj. Mean**[a]	207.48	220.96	209.32	M vs. L	—	0.223**
		95% C.I.**[a]	(192.79, 223.28)	(205.56, 237.52)	(194.06, 225.79)	H vs. L	—	0.866**

TABLE 19-12. (continued)

Adjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
IgM	Officer	n	125	119	117	Overall		0.694
		Adj. Mean[a]	88.92	93.01	93.16	M vs. L	—	0.469
		95% C.I.[a]	(72.88, 108.49)	(76.39, 113.25)	(76.29, 113.77)	H vs. L	—	0.455
	Enlisted Flyer	n	53	62	53	Overall		0.290
		Adj. Mean[a]	111.53	99.29	112.16	M vs. L	—	0.188
		95% C.I.[a]	(98.05, 126.87)	(88.10, 111.90)	(98.59, 127.60)	H vs. L	—	0.951
	Enlisted Groundcrew	n	145	150	138	Overall		0.479
		Adj. Mean[a]	101.29	107.47	102.61	M vs. L	—	0.249
		95% C.I.[a]	(92.35, 111.10)	(97.87, 118.02)	(93.22, 112.94)	H vs. L	—	0.805
Unstimulated PHA Response	Officer	n	50	53	46	Overall		0.335
		Adj. Mean[a]	4,449	3,891	4,430	M vs. L	—	0.201
		95% C.I.[a]	(2,632, 7,521)	(2,359, 6,419)	(2,629, 7,466)	H vs. L	—	0.968
	Enlisted Flyer	n	20	23	25	Overall		0.171
		Adj. Mean[a]	1,477	1,250	1,627	M vs. L	—	0.270
		95% C.I.[a]	(1,070, 2,038)	(907, 1,722)	(1,176, 2,253)	H vs. L	—	0.518
	Enlisted Groundcrew	n	40	63	47	Overall		0.690**
		Adj. Mean**[a]	2,635	2,412	2,529	M vs. L	—	0.395**
		95% C.I.**[a]	(2,173, 3,196)	(2,029, 2,866)	(2,115, 3,025)	H vs. L	—	0.711**

TABLE 19-12. (continued)

Adjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
PHA Net Response (day 1, conc. 1)	Officer	n	50	52	47	Overall		0.433
		Adj. Mean	86,335	98,207	86,596	M vs. L	—	0.265
		95% C.I.	(32,891, 139,779)	(47,238, 149,176)	(33,514, 139,679)	H vs. L	—	0.981
	Enlisted Flyer	n	20	24	25	Overall		0.393
		Adj. Mean	76,112	58,796	78,920	M vs. L	—	0.308
		95% C.I.	(39,658, 112,566)	(22,663, 94,928)	(42,179, 115,661)	H vs. L	—	0.869
	Enlisted Groundcrew	n	42	64	48	Overall		0.525
		Adj. Mean	100,607	95,694	108,737	M vs. L	—	0.675
		95% C.I.	(78,824, 122,390)	(75,980, 115,407)	(88,314, 129,160)	H vs. L	—	0.514
PHA Net Response (day 1, conc. 2)	Officer	n	50	52	47	Overall		0.296
		Adj. Mean	139,055	162,259	148,140	M vs. L	—	0.124
		95% C.I.	(63,435, 214,675)	(90,141, 234,377)	(73,033, 223,249)	H vs. L	—	0.554
	Enlisted Flyer	n	20	24	25	Overall		0.053
		Adj. Mean	149,371	110,819	151,799	M vs. L	—	0.053
		95% C.I.	(107,014, 191,727)	(68,836, 152,801)	(109,110, 194,489)	H vs. L	—	0.902
	Enlisted Groundcrew	n	42	64	48	Overall		0.863
		Adj. Mean	171,479	168,295	176,226	M vs. L	—	0.831
		95% C.I.	(143,737, 199,221)	(143,189, 193,401)	(150,217, 202,236)	H vs. L	—	0.765

TABLE 19-12. (continued)

Adjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
PHA Net Response (day 1, conc. 3)	Officer	n	50	52	47	Overall		0.290
		Adj. Mean	122,226	143,061	133,568	M vs. L	—	0.116
		95% C.I.	(55,726, 188,727)	(79,640, 206,482)	(67,517, 199,619)	H vs. L	—	0.401
	Enlisted Flyer	n	20	24	25	Overall		0.056
		Adj. Mean	143,234	109,316	145,490	M vs. L	—	0.057
		95% C.I.	(105,462, 181,005)	(71,878, 146,754)	(107,421, 183,558)	H vs. L	—	0.898
	Enlisted Groundcrew	n	42	64	48	Overall		0.889
		Adj. Mean	172,265	168,127	165,482	M vs. L	—	0.755
		95% C.I.	(147,577, 196,953)	(145,785, 190,470)	(142,335, 188,629)	H vs. L	—	0.631
PHA Net Response (day 2, conc. 1)	Officer	n	50	54	47	Overall		0.103
		Adj. Mean	146,025	154,299	125,562	M vs. L	—	0.552
		95% C.I.	(75,758, 216,292)	(87,285, 221,313)	(55,721, 195,403)	H vs. L	—	0.151
	Enlisted Flyer	n	20	23	25	Overall		0.226
		Adj. Mean	136,615	102,547	128,967	M vs. L	—	0.111
		95% C.I.	(91,292, 181,937)	(57,467, 147,626)	(83,216, 174,718)	H vs. L	—	0.717
	Enlisted Groundcrew	n	40	63	46	Overall		0.787**
		Adj. Mean**	167,346	157,783	165,018	M vs. L	—	0.521**
		95% C.I.**	(139,776, 194,916)	(133,097, 182,469)	(139,354, 190,682)	H vs. L	—	0.884**

TABLE 19-12. (continued)

Adjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Exposure Index Medium	Exposure Index High	Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
PHA Net Response (day 2, conc. 2)	Officer	n	50	54	47	Overall		0.130
		Adj. Mean	163,115	173,869	149,009	M vs. L	—	0.388
		95% C.I.	(100,237, 225,992)	(113,903, 233,835)	(86,513, 211,506)	H vs. L	—	0.268
	Enlisted Flyer	n	20	23	25	Overall		0.225
		Adj. Mean	161,115	136,315	167,492	M vs. L	—	0.220
		95% C.I.	(118,107, 204,123)	(93,537, 179,092)	(124,077, 210,906)	H vs. L	—	0.750
	Enlisted Groundcrew	n	40	63	46	Overall		0.979
		Adj. Mean	194,693	194,349	197,217	M vs. L	—	0.982
		95% C.I.	(167,086, 222,301)	(169,630, 219,069)	(171,518, 222,916)	H vs. L	—	0.874
PHA Net Response (day 2, conc. 3)	Officer	n	50	54	47	Overall		0.315**
		Adj. Mean**	118,963	124,010	108,261	M vs. L	—	0.636**
		95% C.I.**	(65,096, 172,829)	(72,637, 175,382)	(54,721, 161,801)	H vs. L	—	0.327**
	Enlisted Flyer	n	20	23	25	Overall		0.393
		Adj. Mean	111,834	105,130	127,972	M vs. L	—	0.714
		95% C.I.	(72,694, 150,974)	(66,199, 144,060)	(88,461, 167,482)	H vs. L	—	0.378
	Enlisted Groundcrew	n	40	63	46	Overall		0.780
		Adj. Mean	152,385	148,116	143,553	M vs. L	—	0.716
		95% C.I.	(130,631, 174,140)	(128,637, 167,595)	(123,302, 163,803)	H vs. L	—	0.482

TABLE 19-12. (continued)

Adjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Overall PHA Net Response	Officer	n	49	52	46	Overall		0.320
		Adj. Mean	129,589	142,335	126,748	M vs. L	—	0.255
		95% C.I.	(73,758, 185,420)	(89,096, 195,574)	(71,241, 182,255)	H vs. L	—	0.803
	Enlisted Flyer	n	20	23	25	Overall		0.109
		Adj. Mean	129,862	104,152	133,554	M vs. L	—	0.109
		95% C.I.	(95,920, 163,803)	(70,392, 137,912)	(99,291, 167,817)	H vs. L	—	0.815
	Enlisted Groundcrew	n	40	63	46	Overall		0.860
		Adj. Mean	160,090	154,928	160,093	M vs. L	—	0.650
		95% C.I.	(139,057, 181,124)	(136,095, 173,762)	(140,514, 179,672)	H vs. L	—	0.999
Maximum PHA Net Response	Officer	n	49	52	46	Overall		0.351
		Adj. Mean	188,315	199,596	179,981	M vs. L	—	0.401
		95% C.I.	(169,815, 206,816)	(181,336, 217,856)	(158,967, 200,995)	H vs. L	—	0.547
	Enlisted Flyer	n	20	23	25	Overall		0.122
		Adj. Mean	176,036	149,623	184,617	M vs. L	—	0.149
		95% C.I.	(134,833, 217,239)	(109,261, 189,986)	(143,857, 225,377)	H vs. L	—	0.664
	Enlisted Groundcrew	n	41	63	46	Overall		0.999
		Adj. Mean	219,613	220,208	219,669	M vs. L	—	0.968
		95% C.I.	(196,953, 242,273)	(201,858, 238,559)	(198,322, 241,017)	H vs. L	—	0.997

TABLE 19-12. (continued)

Adjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Unstimulated MLC Response	Officer	n	49	54	47	Overall		0.419
		Adj. Mean[a]	5,102	5,050	4,185	M vs. L	—	0.951
		95% C.I.[a]	(2,189, 11,894)	(2,255, 11,313)	(1,806, 9,699)	H vs. L	—	0.250
	Enlisted Flyer	n	20	23	24	Overall		0.248**
		Adj. Mean**[a]	2,980	2,379	3,613	M vs. L	—	0.382**
		95% C.I.**[a]	(1,725, 5,148)	(1,380, 4,101)	(2,060, 6,338)	H vs. L	—	0.457**
	Enlisted Groundcrew	n	42	62	48	Overall		0.629
		Adj. Mean[a]	6,017	5,172	5,734	M vs. L	—	0.355
		95% C.I.[a]	(4,449, 8,136)	(3,929, 6,809)	(4,320, 7,610)	H vs. L	—	0.780
MLC Net Response	Officer	n	49	54	47	Overall		0.955
		Adj. Mean	89,613	88,876	86,664	M vs. L	—	0.941
		95% C.I.	(39,335, 139,890)	(40,971, 136,781)	(36,739, 136,589)	H vs. L	—	0.773
	Enlisted Flyer	n	20	23	24	Overall		0.201
		Adj. Mean	82,103	69,394	92,162	M vs. L	—	0.332
		95% C.I.	(54,314, 109,891)	(41,725, 97,064)	(63,598, 120,727)	H vs. L	—	0.445
	Enlisted Groundcrew	n	42	62	48	Overall		0.605
		Adj. Mean	92,968	85,497	93,926	M vs. L	—	0.432
		95% C.I.	(75,424, 110,512)	(69,517, 101,477)	(77,469, 110,384)	H vs. L	—	0.924

TABLE 19-12. (continued)

Adjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
NKCA 50/1 Net Response	Officer	n	51	53	48	Overall		0.559
		Adj. Mean	476.5	428.1	441.4	M vs. L	—	0.293
		95% C.I.	(244.0, 709.0)	(206.6, 649.5)	(210.7, 672.2)	H vs. L	—	0.452
	Enlisted Flyer	n	19	24	25	Overall		0.813**
		Adj. Mean**	471.2	495.8	465.1	M vs. L	—	0.658**
		95% C.I.**	(354.7, 587.7)	(380.3, 611.2)	(348.2, 581.9)	H vs. L	—	0.912**
	Enlisted Groundcrew	n	41	62	46	Overall		0.827
		Adj. Mean	432.3	442.7	456.4	M vs. L	—	0.778
		95% C.I.	(363.9, 500.7)	(381.0, 504.4)	(392.2, 520.6)	H vs. L	—	0.541
NKCA 50/1 Percent Release	Officer	n	51	53	48	Overall		0.711
		Adj. Mean	38.0	35.8	35.5	M vs. L	—	0.503
		95% C.I.	(21.2,54.9)	(19.8,51.8)	(18.7,52.2)	H vs. L	—	0.448
	Enlisted Flyer	n	19	24	25	Overall		0.731
		Adj. Mean	37.9	39.5	36.5	M vs. L	—	0.707
		95% C.I.	(28.8,47.0)	(30.5,48.5)	(27.4,45.5)	H vs. L	—	0.738
	Enlisted Groundcrew	n	41	62	46	Overall		0.910**
		Adj. Mean**	36.0	37.1	37.0	M vs. L	—	0.682**
		95% C.I.**	(30.7,41.2)	(32.4,41.9)	(32.1,42.0)	H vs. L	—	0.732**

TABLE 19-12. (continued)

Adjusted Exposure Index for Immunologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
NKCI 50/1 Net Response	Officer	n	50	53	45	Overall		0.243
		Adj. Mean	874.1	868.6	936.8	M vs. L	—	0.900
		95% C.I.	(651.8, 1,096.4)	(656.7, 1,080.5)	(715.4, 1,158.2)	H vs. L	—	0.170
	Enlisted Flyer	n	20	24	25	Overall		0.270
		Adj. Mean	853.5	747.2	821.7	M vs. L	—	0.126
		95% C.I.	(705.3, 1,001.7)	(600.3, 894.1)	(672.4, 971.1)	H vs. L	—	0.646
	Enlisted Groundcrew	n	41	64	48	Overall		0.307
		Adj. Mean	895.5	824.0	874.6	M vs. L	—	0.145
		95% C.I.	(804.6, 986.4)	(742.3, 905.7)	(790.1, 959.1)	H vs. L	—	0.687
NKCI 50/1 Percent Release	Officer	n	50	53	45	Overall		0.688
		Adj. Mean	70.9	69.3	69.5	M vs. L	—	0.421
		95% C.I.	(60.3,81.6)	(59.1,79.4)	(58.9,80.0)	H vs. L	—	0.495
	Enlisted Flyer	n	20	24	25	Overall		0.705
		Adj. Mean	66.3	64.3	66.9	M vs. L	—	0.567
		95% C.I.	(58.9,73.6)	(57.0,71.6)	(59.4,74.3)	H vs. L	—	0.864
	Enlisted Groundcrew	n	41	64	48	Overall		0.801**
		Adj. Mean**	66.1	66.5	67.6	M vs. L	—	0.836**
		95% C.I.**	(62.0,70.1)	(62.9,70.2)	(63.8,71.3)	H vs. L	—	0.521**

TABLE 19-12. (continued)

Adjusted Exposure Index for Immunologic Variables by Occupation

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**Exposure index-by-covariate interaction (0.01<p<0.05)—adjusted mean or relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

—Adjusted relative risk not applicable for continuous analysis of a variable; relative risk/confidence interval/ p-value not given due to cells with zero frequency.

[a]Transformed from natural logarithm scale.

****Exposure index-by-covariate interaction (p<0.01)—adjusted mean or relative risk, confidence interval, and p-value not presented.

[b]Exposure index categories compared on adjusted means of positive cell counts.

TABLE 19-13.

Summary of Exposure Index-by-Covariate Interactions From Adjusted Analyses for Immunologic Variables*

Variable	Occupation	Covariate	p-Value
Composite Skin Test Diagnosis	Officer	Lifetime Cigarette Smoking History	0.017
		Current Alcohol Use	0.018
Composite Skin Test Diagnosis	Enlisted Flyer	Lifetime Alcohol History	0.037
Composite Skin Test Diagnosis	Enlisted Groundcrew	Lifetime Alcohol History	0.002
		Current Alcohol Use	<0.001
CD2 Cells	Enlisted Flyer	Current Alcohol Use	0.001
CD2 Cells	Enlisted Groundcrew	Lifetime Cigarette Smoking History	0.017
CD4 Cells	Enlisted Flyer	Current Alcohol Use	0.035
CD4 Cells	Enlisted Groundcrew	Lifetime Cigarette Smoking History	0.005
CD8 Cells	Officer	Age	0.002
CD8 Cells	Enlisted Flyer	Current Alcohol Use	<0.001
CD8 Cells	Enlisted Groundcrew	Current Alcohol Use	0.012
		Lifetime Alcohol History	0.008
CD20 Cells	Officer	Current Cigarette Smoking	0.013
		Lifetime Cigarette Smoking History	0.009
CD20 Cells	Enlisted Groundcrew	Lifetime Cigarette Smoking History	0.004
CD14 Cells	Enlisted Groundcrew	Lifetime Cigarette Smoking History	0.020
		Current Alcohol Use	0.043
CD25 Cells	Officer	Lifetime Alcohol History	0.012
HLA-DR Cells	Enlisted Groundcrew	Lifetime Cigarette Smoking History	0.011
CD4/CD8 Ratio	Officer	Age	<0.001
CD4/CD8 Ratio	Enlisted Groundcrew	Current Alcohol Use	0.015
TLC	Enlisted Groundcrew	Lifetime Cigarette Smoking History	0.004
IgG	Enlisted Groundcrew	Lifetime Cigarette Smoking History	0.001
IgA	Officer	Current Cigarette Smoking	0.032
IgA	Enlisted Groundcrew	Lifetime Alcohol History	0.012
Unstimulated PHA Response	Enlisted Groundcrew	Current Alcohol Use	0.047
		Lifetime Alcohol History	0.027
PHA Net Response (day 2, conc. 1)	Enlisted Groundcrew	Age	0.035
PHA Net Response (day 2, conc. 3)	Officer	Current Cigarette Smoking	0.014

TABLE 19-13. (continued)

Summary of Exposure Index-by-Covariate Interactions
From Adjusted Analyses for Immunologic Variables*

Variable	Occupation	Covariate	p-Value
Unstimulated MLC Response	Enlisted Flyer	Age	0.046
NKCA 50/1 Net Response	Enlisted Flyer	Lifetime Cigarette Smoking History	0.015
NKCA 50/1 Percent Release	Enlisted Groundcrew	Age	0.014
NKCI 50/1 Percent Release	Enlisted Groundcrew	Age	0.042

*Refer to Table P-4 for a further investigation of these interactions.

The final interpretation of the exposure index data must await the reanalysis of the clinical data using the results of the serum dioxin assay. The report is expected in 1991.

Physical Examination Data

Composite Skin Test Diagnosis

For officers and for enlisted flyers, the unadjusted overall exposure index analyses comparing the relative frequencies of participants with possibly abnormal skin test reactions for the composite skin test diagnosis were borderline significant ($p=0.090$ and $p=0.100$, respectively). For the officers, the high versus low exposure contrast was borderline significant ($p=0.073$), with the low exposure category having a higher percentage of participants with possibly abnormal readings (8.6%) than the high exposure category (2.0%). For the enlisted flyers, the medium versus low exposure contrast was also borderline significant ($p=0.083$), with the low exposure category having a higher percentage of participants with possibly abnormal readings (15.0%) than the medium exposure category (2.3%). Although the unadjusted overall exposure index analysis for the enlisted groundcrew was not significant, the medium versus low exposure contrast was borderline significant ($p=0.087$), with the medium exposure category having a higher percentage of participants with possibly abnormal readings (12.4%) than the low exposure category (5.1%).

For officers, the adjusted exposure index analysis of the composite skin test diagnosis had a significant exposure index-by-lifetime cigarette smoking history interaction ($p=0.017$) and a significant exposure index-by-current alcohol use interaction ($p=0.018$). Because of these interactions, the two covariates were trichotomized and contrasts performed within combinations of the covariate strata. For Ranch Hand officers with over 10 pack-years lifetime cigarette smoking history and a current alcohol use of zero to one drink per day, the relative frequency of participants with a possibly abnormal composite skin test was significant ($p=0.035$). The contrast of the high exposure category versus the low exposure category was marginally significant ($p=0.083$; 0.0% and 16.7%, respectively). Without the significant interactions of exposure index-by-lifetime cigarette smoking history and exposure index-by-current alcohol use in the adjusted model, a marginally significant contrast for the high exposure group versus the low exposure group ($p=0.070$) resulted; however, the contrast was not consistent with a dose-response relationship between exposure category and percent possibly abnormal.

For the Ranch Hand enlisted flyers, the adjusted exposure index analysis had a significant exposure index-by-lifetime alcohol history interaction ($p=0.037$). Because of this interaction, lifetime alcohol history was trichotomized on participants with lifetime alcohol history values of 0 drink-years, at most 40 drink-years, and over 40 drink-years. For Ranch Hand enlisted flyers with lifetime alcohol history values over 40 drink-years, the relative frequency of participants having possibly abnormal composite skin test results differed significantly ($p=0.049$) for the low, medium, and high exposure groups (25%, 0%, and 0%, respectively). An adjusted analysis without the exposure index-by-lifetime alcohol history interaction in the model was significant ($p=0.014$).

For the Ranch Hand enlisted groundcrew, the adjusted exposure index model contained two significant interactions: exposure index-by-lifetime alcohol history ($p=0.002$) and exposure index-by-current alcohol use ($p<0.001$). Because of these interactions, the two covariates were trichotomized and contrasts performed within combinations of the covariate strata. For Ranch Hand enlisted groundcrew with lifetime alcohol history values above 40 drink-years and current alcohol use between zero and one drink per day, the relative frequencies of participants with possibly abnormal composite skin test results differed significantly ($p=0.034$) across the low, medium, and high exposure groups (9.1%, 36.4%, and 0.0%, respectively).

None of these analyses was consistent with an expected dose-response relationship since the low dose category in all three analyses had a higher percentage of possibly abnormal skin test diagnoses than the high category.

Laboratory Examination Data: Quantitative Studies--Cell Surface Marker (Phenotypic) Studies

CD2 Cells

The unadjusted average CD2 cell counts were not significantly different among the exposure index categories in all three occupational categories.

For officers, the adjusted exposure index analysis of the CD2 cell counts was not significant.

The adjusted exposure index analysis for the enlisted flyers had a significant exposure index-by-current alcohol use interaction ($p=0.001$). To investigate this interaction, current alcohol use was dichotomized as zero or one drink per day, and over one drink per day. For both strata, neither the medium versus low exposure contrast nor the high versus low exposure contrast was significant.

For enlisted groundcrew, the adjusted exposure index analysis had a significant exposure index-by-lifetime cigarette smoking history interaction ($p=0.017$). This interaction was investigated for the lifetime cigarette smoking history categories of 0 pack-years, at most 10 pack-years, and over 10 pack-years. For those Ranch Hand enlisted groundcrew with lifetime cigarette smoking values not exceeding 10 pack-years, the difference in the adjusted CD2 means for the low versus high exposure contrast was significant (1,789.3 cells/mm^3 vs. 1,308.9 cells/mm^3, respectively; $p=0.010$). For those Ranch Hand enlisted groundcrew having lifetime cigarette smoking values over 10 pack-years, the adjusted mean CD2 level for the high exposure group was marginally greater than the low exposure group (1,908.9 cells/mm^3 vs. 1,522.5 cells/mm^3; $p=0.061$). An adjusted analysis performed without the exposure index-by-lifetime cigarette smoking history interaction was not significant.

CD4 Cells

Stratifying by occupation, the unadjusted analyses of the CD4 cell counts showed no significant differences among the exposure index categories.

However, within the officer occupational strata, the medium versus low exposure contrast was marginally significant (p=0.100), with unadjusted CD4 means of 932.3 cells/mm^3 and 823.2 cells/mm^3, respectively.

For officers, the adjusted exposure index analysis of the CD4 cell counts was not significant.

For enlisted flyers, the adjusted exposure index analysis contained a significant exposure index-by-current alcohol use interaction (p=0.035). Exposure level contrasts were performed within dichotomized current alcohol use categories: zero to one drink per day, and over one drink per day. Within each of these strata, the adjusted CD4 means for the medium versus low exposure contrast and the high versus low contrast were not significant. For the enlisted flyers, an adjusted analysis of the CD4 counts, without the exposure index-by-current alcohol use interaction, was not significant.

For the enlisted groundcrew, the adjusted exposure index analysis had a significant exposure index-by-lifetime cigarette smoking history interaction (p=0.005). To explore the interaction, lifetime cigarette smoking history was categorized into 0 pack-years, at most 10 pack-years, and over 10 pack-years. For those Ranch Hand enlisted groundcrew with at most 10 pack-years smoking history, the high versus low exposure contrast of the adjusted CD4 means was significant (734.5 cells/mm^3 vs. 1,058.3 cells/mm^3, respectively; p=0.004).

CD8 Cells

The unadjusted exposure index analyses of the CD8 cell counts had no significant differences for any of the occupations.

For officers, the adjusted exposure index analysis of the CD8 cell counts had a significant exposure index-by-age interaction (p=0.002). To investigate this interaction, exposure index contrasts were performed within each of the following age strata: participants born in or after 1942, participants born between 1923 and 1941, and participants born in or before 1922. For the youngest category of Ranch Hand officers, the adjusted mean CD8 level for the high exposure level was greater than that of the low exposure level (690.7 cells/mm^3 vs. 405.5 cells/mm^3; p=0.015). For the oldest group of Ranch Hand officers, significant adjusted mean CD8 levels were found for the medium versus low exposure contrast (399.2 cells/mm^3 vs. 1,121.9 cells/mm^3, respectively; p<0.001) and the high versus low exposure contrast (466.1 cells/mm^3 vs. 1,121.9 cells/mm^3, respectively; p=0.036).

For the enlisted flyer Ranch Hands, the adjusted exposure index analysis of the CD8 cell counts had a significant exposure index-by-current alcohol use interaction (p<0.001). This interaction was explored by stratifying current alcohol use into two strata and contrasting exposure index groups on the adjusted mean CD8 levels within each of the strata. For Ranch Hand enlisted flyers not exceeding one drink per day, the adjusted CD8 mean for the high exposure level was greater than the mean of the low exposure level (674.9 cells/mm^3 vs. 499.6 cells/mm^3; p=0.044). For the Ranch Hand enlisted flyers having over one drink per day, the adjusted mean CD8 levels differed between the medium versus low exposure categories (569.6 cells/mm^3 vs. 244.2 cells/mm^3, respectively; p=0.015).

For the Ranch Hand enlisted groundcrew, the adjusted exposure index analysis had two significant interactions: exposure index-by-lifetime alcohol history ($p=0.008$) and exposure index-by-current alcohol use ($p=0.012$). These interactions were investigated by stratifying both of the alcohol use covariates. For those Ranch Hand enlisted groundcrew with lifetime alcohol history values above 40 drink-years and current alcohol use not exceeding one drink per day, the adjusted mean CD8 level of the medium exposure level was marginally greater than the low exposure level (572.0 cells/mm^3 vs. 339.3 cells/mm^3; $p=0.060$).

CD20 Cells

For each occupation, the unadjusted exposure index analysis of the CD20 cell counts displayed no significant differences.

For Ranch Hand officers, the adjusted exposure index analysis of the CD20 counts had a significant exposure index-by-lifetime cigarette smoking history interaction ($p=0.009$) and a significant exposure index-by-current cigarette smoking interaction ($p=0.013$). Because of these interactions, both of the smoking covariates were stratified and contrasts performed within the combined strata. For each of the strata combinations, the adjusted means for the CD20 cell counts of the medium exposure versus low exposure groups, and the high versus low exposure groups, were not significant.

For Ranch Hand enlisted flyers, the adjusted exposure index analysis of the CD20 cell counts was not significant.

For Ranch Hand enlisted groundcrew, the adjusted exposure index analysis of the CD20 cells had a significant exposure index-by-lifetime cigarette smoking history interaction ($p=0.004$). As a followup to this interaction, exposure index contrasts were performed within the following strata of the lifetime smoking covariate: 0 pack-years, over 0 pack-years and at most 10 pack-years, and over 10 pack-years. Within the 0 pack-year strata, the adjusted mean CD20 level for the medium exposure category was marginally lower than the mean CD20 level of the low exposure category (134.3 cells/mm^3 vs. 206.4 cells/mm^3; $p=0.059$). For the middle smoking history strata, the high versus low exposure contrast was significant ($p=0.049$). The low exposure level had a higher adjusted mean than the high exposure level (227.5 cells/mm^3 vs. 158.0 cells/mm^3). For Ranch Hand enlisted groundcrew with over 10 pack-years smoking history, the medium versus low exposure contrast was marginally significant ($p=0.077$) and the high versus low exposure contrast was significant ($p=0.014$). Within the over 10 pack-year lifetime cigarette smoking history strata, the adjusted mean CD20 levels exhibited a dose-response relation with the exposure index (low: 150.9 cells/mm^3; medium: 204.5 cells/mm^3; high: 238.7 cells/mm^3).

CD14 Cells

For the unadjusted exposure index analyses of the CD14 cell counts, the enlisted flyers displayed a borderline significant difference ($p=0.078$). The unadjusted means were inversely related to the exposure index (low, 39.4 cells/mm^3; medium, 29.8 cells/mm^3; high, 22.9 cells/mm^3). The contrast

of high exposure versus low exposure of the CD14 cell counts was significant ($p=0.025$) for the enlisted flyers. No other unadjusted exposure index analyses were significant.

For Ranch Hand officers, the adjusted exposure index analysis of the CD14 cell counts was not significant.

For Ranch Hand enlisted flyers, the adjusted means of the CD14 cell counts did not differ significantly among exposure index categories. However, the high exposure versus low exposure contrast was borderline significant (20.3 cells/mm^3 vs. 32.0 cells/mm^3, respectively; $p=0.075$).

The adjusted exposure index analysis for the Ranch Hand enlisted groundcrew contained a significant exposure index-by-lifetime cigarette smoking history interaction ($p=0.020$) and a significant exposure index-by-current alcohol use interaction ($p=0.043$). To explore these interactions, current alcohol use was dichotomized as zero or one drink per day and over one drink per day and lifetime cigarette smoking history was dichotomized as at most 10 pack-years and over 10 pack-years. For Ranch Hand enlisted groundcrew with lifetime cigarette smoking history values of at most 10 pack years and a current alcohol use value of zero to one drink per day, the adjusted mean for the medium exposure level (19.5 cells/mm^3) was significantly different ($p=0.036$) from that of the low exposure level (29.4 cells/mm^3). For Ranch Hand enlisted groundcrew with lifetime cigarette smoking history values over 10 pack-years and a current alcohol use value of zero or one drink per day, the medium exposure versus low exposure contrast was significant (36.5 cells/mm^3 and 21.6 cells/mm^3, respectively; $p=0.023$). Without the two specified interaction terms in the adjusted model, the adjusted exposure index analysis was not significant. No consistent patterns were evident in these interactions.

CD25 Cells

For the CD25 cell counts, the unadjusted exposure index analyses were not significant for any of the occupations. Similar to the core analyses, both the proportions of zero CD25 values and the means of the positive CD25 values were compared across exposure index categories. For the former, there were no significant differences in the proportions of zero CD25 values across exposure category for any occupation. For the latter, the high versus low exposure contrast was borderline significant (low, 13.8 cells/mm^3; medium, 11.1 cells/mm^3; high, 9.3 cells/mm^3; $p=0.095$) for the enlisted groundcrew.

For the Ranch Hand officers, the adjusted exposure index analysis on positive CD25 values had a significant exposure index-by-lifetime alcohol history interaction ($p=0.012$). The lifetime alcohol history covariate was trichotomized as 0 drink-years, not more than 40 drink-years, and over 40 drink-years. Within each of these strata, the adjusted mean CD25 levels were contrasted for medium versus low exposure and for high versus low exposure. For those Ranch Hand officers with over 40 drink-years for lifetime alcohol history, the high versus low exposure contrast of the adjusted CD25 means was borderline significant (46.5 cells/mm^3 vs. 12.7 cells/mm^3, respectively; $p=0.051$). Exposure index analyses were not significant without the exposure index-by-lifetime alcohol history interaction term in the adjusted model.

For both the Ranch Hand enlisted flyers and the enlisted groundcrew, no significant differences were found for the adjusted exposure index analysis of the positive CD25 cell counts.

HLA-DR Cells

For the unadjusted exposure index analysis of the HLA-DR cell counts, the overall exposure index comparisons were not significant for any of the occupations. However, for the enlisted flyers, the high versus low exposure contrast of the average HLA-DR cell counts was borderline significant and exhibited a dose-response relationship (low, 504.1 cells/mm^3; medium, 416.1 cells/mm^3; high, 389.0 cells/mm^3; p=0.069).

For the Ranch Hand officers and the enlisted flyers, the adjusted exposure index analyses of the HLA-DR cell counts were not significant.

For the Ranch Hand enlisted groundcrew, the adjusted exposure index analysis of the HLA-DR cell counts contained a significant exposure index-by-lifetime cigarette smoking history interaction (p=0.011). After lifetime cigarette smoking history was trichotomized as 0 pack-years, not more than 10 pack-years, and over 10 pack-years, adjusted HLA-DR means were compared within each strata. For the zero pack-year strata, the adjusted HLA-DR cell mean contrast for the medium versus low exposure categories was significant (325.4 cells/mm^3 vs. 475.3 cells/mm^3, respectively; p=0.013). For the middle lifetime cigarette smoking history category, the high versus low exposure contrast was significant (369.7 cells/mm^3 vs. 491.5 cells/mm^3, respectively; p=0.022). For Ranch Hand enlisted groundcrew with over 10 pack-years lifetime cigarette smoking history, the adjusted HLA-DR mean for the medium exposure category was marginally greater (p=0.059) than the HLA-DR mean for the low exposure category, and the adjusted mean for the high exposure category was significantly greater (p=0.010) than the adjusted mean for the low exposure category (low: 383.9 cells/mm^3; medium: 476.9 cells/mm^3; high: 528.6 cells/mm^3). An adjusted analysis, performed without the exposure index-by-lifetime cigarette smoking history interaction, was not significant.

CD4/CD8 Ratio

No significant differences were found for the unadjusted exposure index analyses of the CD4/CD8 ratio values.

For the Ranch Hand officers, the adjusted exposure index analysis of the CD4/CD8 ratios had a significant exposure index-by-age interaction (p<0.001). Age was trichotomized as participants born in or after 1942, born between 1923 and 1941, and born in or before 1922 for investigation of this interaction. For the oldest Ranch Hand officers, the adjusted means for the CD4/CD8 ratios differed between the medium and low exposure groups (p=0.001) and between the high and low exposure groups (p=0.044). For these Ranch Hand officers, the adjusted CD4/CD8 ratio means for the low, medium, and high exposure groups were 0.54, 1.57, and 1.30, respectively.

For the Ranch Hand enlisted flyers, the adjusted overall exposure index analysis of the CD4/CD8 ratios was not significant. However, the contrast of

the adjusted means for the high exposure versus low exposure groups was borderline significant (1.58 vs. 1.98, respectively; p=0.080).

For the Ranch Hand enlisted groundcrew, the exposure index-by-current alcohol use interaction was significant (p=0.015) for the CD4/CD8 ratios. Because of this interaction, current alcohol use was dichotomized as zero to one drink per day, and over one drink per day. For those Ranch Hand enlisted groundcrew having more than one drink per day, the adjusted CD4/CD8 mean for the high exposure level differed marginally from the adjusted CD4/CD8 mean of the low exposure level (6.80 vs. 2.04, respectively; p=0.067). Exposure index analyses were not significant without the interaction term in the model.

Laboratory Examination Data: Quantitative Studies--TLC

No differences were detected in the unadjusted and adjusted analyses of the officer and enlisted flyer cohorts. In the unadjusted analysis of the enlisted groundcrew cohort, there was a significant exposure index-by-lifetime cigarette smoking history interaction (p=0.004). Stratifying by lifetime cigarette smoking history, a significant difference (p=0.031) in the high versus low contrast was found for Ranch Hand smokers with a history of 10 pack-years or less and a marginally significant difference (p=0.058) in the high versus low exposure contrast for Ranch Hand smokers with a history of over 10 pack-years.

Laboratory Examination Data: Quantitative Studies--Quantitative Immunoglobulins

IgG

There were no significant differences identified in the unadjusted exposure index analyses of IgG. The adjusted analyses of the enlisted flyer cohort also revealed no significant differences.

In the adjusted analysis of the officer cohort, the overall and high versus low exposure contrasts were significant (p=0.032 and p=0.012, respectively). The adjusted means were 962.6 mg/dl, 1,032.7 mg/dl, and 1.242.6 mg/dl, for the low, medium, and high exposure categories, respectively.

For the enlisted groundcrew cohort, there was a significant exposure index-by-lifetime cigarette smoking history interaction (p=0.001). Stratifying by lifetime cigarette smoking history revealed a significant difference in the nonsmokers for the high versus low exposure contrast (adjusted means: 1,148.3 mg/dl for low, 1,208.2 mg/dl for medium, and 1,278.7 mg/dl for high; p=0.036). The high versus low exposure contrast for the heavy smokers was borderline significant (adjusted means: 1,219.3 mg/dl for low, 1,178.3 mg/dl for medium, and 1,149.7 mg/dl for high; p=0.086).

IgA

No significant differences were detected in the unadjusted analysis of the officer cohort. There were also no differences identified in the adjusted analysis without a significant exposure index-by-current cigarette smoking interaction (p=0.032). After stratifying by current smoking, the high versus low exposure contrast for the nonsmokers was significant (p=0.019), and the medium versus low exposure contrast was borderline significant (p=0.085). The adjusted means for the nonsmoking officers were 232.97 mg/dl, 196.15 mg/dl, and 184.98 mg/dl for the low, medium, and high exposure categories, respectively. The medium versus low exposure contrast for the heavy smokers was also significant (adjusted means: 228.23 mg/dl for low, 125.91 mg/dl for medium, and 185.50 mg/dl for high; p=0.002).

In the unadjusted analysis of the enlisted flyer cohort, the medium versus low exposure contrast was marginally significant (p=0.091). The mean of the low exposure category was 225.57 mg/dl, as compared to means of 195.85 mg/dl and 215.75 mg/dl for the medium and high exposure categories, respectively. The medium versus low exposure contrast of the adjusted analysis of the enlisted flyer cohort was also marginally significant (p=0.091).

For the enlisted groundcrew cohort, no differences were detected in the unadjusted analysis. In the adjusted analysis, there was a significant exposure index-by-lifetime alcohol history interaction (p=0.012). Stratifying by lifetime alcohol history to explore the interaction revealed no significant differences. Without the exposure index-by-lifetime alcohol history interaction in the model, there were no significant differences.

IgM

The unadjusted and adjusted exposure index analyses of IgM did not reveal any significant differences among exposure levels for the three occupational cohorts.

Laboratory Examination Data: Functional Stimulation Tests

Unstimulated PHA Responses

For each occupation, the unstimulated PHA responses of day 1 and day 2 were analyzed concurrently to assess differences among exposure index categories. The unadjusted exposure index analysis was performed using a two-factor model (containing exposure index, day, and exposure index-by-day interaction terms) assuming repeated measures across one factor (day). For each occupation, there were no significant differences among the unstimulated mean PHA responses of the high, medium, and low exposure index categories.

For the adjusted exposure index repeated measures analysis of the day 1 and day 2 unstimulated PHA responses, neither the officers nor the enlisted flyers had significant differences among the exposure index categories. For the enlisted groundcrew, the adjusted model had a significant exposure

index-by-current alcohol use interaction (p=0.047) and a significant exposure index-by-lifetime alcohol history interaction (p=0.027). Stratifying by current alcohol use and lifetime alcohol history, Ranch Hands having at most one drink per day and lifetime alcohol history above 40 drink-years had a significant medium versus low exposure contrast (1,767 cpm vs. 3,708 cpm, respectively; p=0.012). The adjusted analysis for the enlisted groundcrew was repeated without the two interaction terms included in the model. The adjusted means were not significantly different among the exposure index categories for this secondary model.

PHA Net Response for Day 1 at Concentration Level 1

For the PHA net responses for day 1 at concentration level 1, both the unadjusted and the adjusted analyses displayed no significant differences across exposure index categories for any occupation.

PHA Net Response for Day 1 at Concentration Level 2

For each occupation, the overall unadjusted exposure index comparisons of the PHA net responses for day 1 at concentration level 2 were not significant. However, among the enlisted flyers group, the medium versus low exposure contrast was marginally significant (low, 173,558 cpm; medium, 136,739 cpm; high, 171,800 cpm; p=0.077).

For the adjusted exposure index analysis, the enlisted flyers exhibited a borderline significant difference (p=0.053) on the PHA net responses for day 1 at concentration level 2. The average net responses for the low, medium, and high exposure groups were 149,371 cpm, 110,819 cpm, and 151,799 cpm, respectively. The medium versus low exposure contrast was borderline significant (p=0.053). Adjusted exposure index analyses for both the officers and the enlisted groundcrew were not significant for the PHA net responses of day 1 at concentration level 2.

PHA Net Response for Day 1 at Concentration Level 3

For enlisted flyers, the unadjusted exposure index analysis of the PHA net responses for day 1 at concentration level 3 was marginally significant (p=0.067). For the enlisted flyers, the medium versus low exposure contrast was significant (low, 165,631 cpm; medium, 126,209 cpm; high, 158,427 cpm; p=0.033). Neither the officers nor the enlisted groundcrew had significant unadjusted exposure index analyses for the PHA net responses for day 1 at concentration level 3.

The enlisted flyers had a borderline significant difference (p=0.056) for the overall exposure index analysis of the PHA net responses for day 1 at concentration level 3. The average net responses for the low, medium, and high exposure groups were 143,234 cpm, 109,316 cpm, and 145,490 cpm, respectively. The medium versus low exposure contrast was also borderline significant (p=0.057). Adjusted exposure index analyses for both the officers and the enlisted groundcrew were not significant for the PHA net responses of day 1 at concentration level 3.

PHA Net Response for Day 2 at Concentration Level 1

For the unadjusted exposure index analysis of the PHA net responses for day 2 at concentration level 1, no significant differences were found for any of the occupations.

For the adjusted exposure index analysis of the PHA net responses for day 2 at concentration level 1, no significant differences were found for either the officers or the enlisted flyers. For the enlisted groundcrew, the adjusted exposure index analysis had a significant exposure index-by-age interaction (p=0.035). To explore this interaction, age was dichotomized into those participants born in or after 1942 and those born before 1942. Within each age stratum, no significant contrasts were found. Without the exposure index-by-age interaction, the adjusted analysis for the enlisted groundcrew showed no significant difference for exposure index.

PHA Net Response for Day 2 at Concentration Level 2

For each occupation, the unadjusted and the adjusted exposure index analyses of the PHA net responses for day 2 at concentration level 2 were not significant.

PHA Net Response for Day 2 at Concentration Level 3

Unadjusted exposure index analyses of the PHA net responses for day 2 at concentration level 3 were not significantly different for any occupation.

For Ranch Hand enlisted flyers and enlisted groundcrew, the adjusted exposure index analysis of the PHA net responses for day 2 at concentration level 3 were not significant. For the Ranch Hand officers, the adjusted model had a significant exposure index-by-current cigarette smoking interaction (p=0.014). To investigate this interaction, the smoking covariate was stratified into four categories: 0 cigarettes per day--never smoked, 0 cigarettes per day--formerly smoked, at most 20 cigarettes per day, and over 20 cigarettes per day. For Ranch Hand officers who were former smokers, the adjusted mean PHA net response for the high exposure category was significantly lower than the mean for the low exposure category (94,234 cpm vs. 130,372 cpm; p=0.023). Also, for Ranch Hand officers who smoked over 20 cigarettes per day, the adjusted mean PHA net response for the medium exposure category was greater than that of the low exposure category (178,503 cpm vs. 81,091 cpm; p=0.003). An adjusted analysis performed without the interaction in the model did not result in a significant difference among exposure index categories.

Overall PHA Net Response

For the six PHA net responses of day 1 and day 2 at each of three concentration levels, unadjusted exposure index analyses were performed for each occupation assuming a three-factor repeated measures analysis framework (exposure index, day, concentration, associated two-factor interactions, and a three-factor interaction). The overall exposure index contrast was not significant for any of the occupations.

For the adjusted analysis using covariate information, the three-factor repeated measures analysis of all six PHA net responses simultaneously exhibited no significant difference across exposure category by occupation.

Maximum of Day and Concentration Level PHA Net Response

No significant differences were found in the unadjusted analyses or the adjusted analyses of each occupational cohort.

Unstimulated MLC Response

For each occupation, the unadjusted exposure index analyses were not significant for the unstimulated MLC responses.

For the Ranch Hand officers and enlisted groundcrew, the adjusted exposure index analysis comparisons of the unstimulated MLC response adjusted means were not significant across the low, medium, and high exposure categories. For enlisted flyers, the adjusted exposure index analysis had a significant exposure index-by-age interaction ($p=0.046$). Because of this interaction, age was dichotomized as participants born in or after 1942 and those born before 1942. Within each age stratum, there were no significant differences for either the medium versus low exposure contrast or the high versus low exposure contrast. An adjusted exposure index model was also used without the exposure index-by-age interaction term included. No significant differences were found for the overall contrast or the paired contrasts of medium versus low exposure and high versus low exposure for this secondary model.

MLC Net Response

For each occupation, the unadjusted and adjusted exposure index analyses of the MLC net responses did not display significant differences for either the overall contrast or the paired contrasts of medium versus low exposure and high versus low exposure.

NKCA 50/1 Net Response

For the NKCA 50/1 net response, the unadjusted exposure index analysis displayed no significant differences for any occupation.

For both Ranch Hand officers and enlisted groundcrew, the adjusted exposure index analysis of the NKCA 50/1 net response was not significant. For Ranch Hand enlisted flyers, the adjusted model contained a significant exposure index-by-lifetime cigarette smoking history interaction ($p=0.015$). Because of this interaction, exposure index contrasts were performed within each of three categorized levels of the lifetime cigarette smoking history covariate (0 pack-years, over 0 pack-years to 10 pack-years, and over 10 pack-years). For Ranch Hand enlisted flyers who had never smoked, the adjusted mean of the NKCA net response for the high exposure level was marginally less than the adjusted mean of the low exposure level (316.3 cpm

vs. 589.2 cpm; p=0.051). For Ranch Hand enlisted flyers with at most 10 pack-years lifetime smoking history, the adjusted mean of the medium exposure level was marginally greater than the adjusted mean of the low exposure level (571.4 cpm vs. 376.8 cpm; p=0.066). Without the exposure index-by-lifetime cigarette smoking history interaction in the adjusted model, the exposure index was not significant for the enlisted flyers.

NKCA 50/1 Percent Release

For each of the three occupations, the unadjusted exposure index analysis exhibited no significant differences for the NKCA 50/1 percent release.

For Ranch Hand officers and enlisted flyers, there were no significant differences for the adjusted exposure index analysis of the NKCA 50/1 percent release. However, for the Ranch Hand enlisted groundcrew, the adjusted model contained a significant exposure index-by-age interaction (p=0.014). As a result of that interaction, exposure index contrasts were performed within dichotimized strata of the age covariate (participants born in or after 1942 and those born before 1942). For those born before 1942, the adjusted mean percent release for the medium exposure category was significantly greater than the adjusted mean of the low exposure category (43.1 vs. 32.8; p=0.041). Without the exposure index-by-age interaction, the adjusted analysis was not significant.

NKCI 50/1 Net Response

For each of the three occupations, the unadjusted exposure index analyses for the NKCI 50/1 net response was not significant. However, for officers, the high versus low exposure index contrast was borderline significant (p=0.069).

For each occupation, the adjusted exposure index analyses of the NKCI net response were not significant.

NKCI 50/1 Percent Release

For the NKCI 50/1 percent release, the unadjusted exposure index analyses were not significant for each occupation.

For the Ranch Hand officers and enlisted flyers, the adjusted exposure index analyses of the NKCI percent releases were not significant. For the Ranch Hand enlisted groundcrew, there was a significant exposure index-by-age interaction (p=0.042). Age was dichotomized into participants born in or after 1942 and those born before 1942. For the latter stratum, the adjusted mean percent release of the medium exposure level was marginally greater than the adjusted mean of the low exposure level (71.4 vs. 64.9; p=0.094). An adjusted exposure index analysis was performed without the exposure index-by-age interaction in the model was not significant.

TABLE 19-14.

Longitudinal Analysis of CD4/CD8 Ratio:
A Contrast of 1985 Followup and 1987 Followup Examination Means

Variable	Examination	Group Means*		p-Value* (Equality of Differences)
		Ranch Hand	Comparison	
CD4/CD8 Ratio	1985 Followup	1.63	1.60	0.908
	1987 Followup	1.94	1.91	

Note: Summary statistics for the 1985 followup and the 1987 followup are based on 318 Ranch Hands and 417 Comparisons who took the immunologic examination at both the 1985 and 1987 followup examinations.

*Means transformed from the natural logarithm scale; hypothesis test performed on the natural logarithm scale.

Longitudinal Analysis

For the immunology assessment, the CD4/CD8 ratio was analyzed (unadjusted for any covariates) for longitudinal differences between the 1985 followup and the 1987 followup examinations. Table 19-14 shows that there was no significant difference in the change over time between Ranch Hands and Comparisons (p=0.908).

DISCUSSION

Immunologic competence was assessed by analysis of data from cell surface marker studies, immunoglobulin quantitation, functional stimulation assays, and skin tests for delayed hypersensitivity response on a randomized subset of the study population. The tuberculin skin test is the prototype test for DCH. This test has been used throughout the 20th century as the traditional method of diagnosing infection with Mycobacterium tuberculosis in individual patients, contacts of diseased individuals, occupational groups, and epidemiologic studies of populations.

The absence of a response to a series of skin test antigens is usually indicative of an impaired immune defense mechanism (anergy). Anergy can occur in elderly individuals in the setting of certain viral, bacterial, and fungal infections; or with advanced protein deficiency, underlying malignancy, or treatment with corticosteroids and other immunosuppressive agents. Skin tests for DCH are occasionally used to test for anergy as a prognostic indicator in individuals in compromised states such as the acquired immunodeficiency syndrome or those at risk of infection following surgery.

Skin tests for DCH are subject to numerous variables including the dose and method of administration of the antigen and the techniques employed in reading and interpreting the response. Following quality control concerns over the 1985 skin test data, stringent protocols were established to ensure consistent methods and interpretation. In the current study, a premium was placed on uniform and consistent methods and interpretation. There was a 92 percent concordance between readers and duplicate interpretations by the same reader. More than 99.6 percent of the sample population had interpretable skin tests. The 94.9 percent incidence of intact DCH is consistent with clinical experience in the general population. Analysis of the data suggested interactive effects of cigarette and alcohol use. Clarification of the observed group difference in the composite skin test diagnosis must await the analysis of the quantitative serum dioxin results.

Cell surface marker studies for CD2 (total T cell), CD4 (helper T cell), CD8 (suppressor T cell), CD25 (activated T cells), CD20 (total B cell), CD14 (monocytes), and HLA-DR positive cell populations were analyzed. The CD4/CD8 ratio was calculated and also analyzed. Both the unadjusted and adjusted analyses of the various cell surface markers measured did not indicate significant group differences between Ranch Hands and Comparisons. Significant covariate associations with age were found for CD2, CD4, CD8, CD20, and HLA-DR cells. These variables consistently decreased with increasing age, which is consistent with established clinical findings. Statistically significant race and alcohol associations were found for CD20 and CD14. Overall, cell surface marker counts increased with cigarette smoking. The clinical significance of these findings is unknown.

Functional stimulation assay data analyzed include the unstimulated and stimulated responses for both the PHA and MLC assays. No significant unadjusted or adjusted group differences between Ranch Hands and Comparisons were found for either the PHA or MLC assays. Both PHA and MLC responses appeared to decrease with age. Race appeared to affect PHA response, but biologic significance was difficult to evaluate given the lack of established clinical endpoints associated with these differences and the lack of a consensus as to what the normal range is for these assays. Implications of mild to moderate increases and decreases are not known. The ability to respond to a challenge with increased cell counts and functional reactions is desirable but a hyperactive response may not be desirable since it might indicate a constantly challenged immune system.

Other functional stimulation assay data evaluated included the net responses for the natural killer cell assays (with and without the addition of Interleukin 2 as a response stimulator). Unadjusted analyses for both natural killer cell assays revealed no significant Ranch Hand and Comparison differences; however, there was a significant group-by-race interaction for both assays. When analyzing the data within each racial grouping, there was a statistically significant difference between Black Ranch Hands and Black Comparisons.

The adjusted group contrast analysis for the four natural killer cell variables and the MLC net response variable each contained group-by-race interactions. The clinical significance of these findings is not apparent.

The exposure index analyses failed to reveal any consistent trends in the many variables analyzed. For the adjusted analyses, many exposure index-by-covariate interactions were found. These interactions primarily involved the covariates of cigarette smoking, age, and alcohol use. Final interpretation of these data must await the results of the serum TCDD assays and the development of interpretive criteria for these immunologic assays.

As seen in the 1985 followup, there were no significant group differences for either the unadjusted or adjusted analyses of any of the laboratory immunologic variables examined. Consistently decreasing values for the cell surface markers and functional stimulation assays were associated with increasing age, while increases in lifetime smoking were usually associated with increases in the values of those variables. Longitudinal analysis of the CD4/CD8 ratio results did not reveal a significant group difference over time.

In summary, the immunologic assessment of laboratory data revealed no statistically significant differences between the Ranch Hand and Comparison populations. Covariate associations with age and lifetime smoking were noted in the adjusted analyses of these immunologic tests. The finding of a group difference in the proportion of participants possibly abnormal on the composite skin test diagnosis is of interest and will be reevaluated in the context of quantitative serum dioxin levels. Overall, there appears to be no indication of impaired immunologic competence in the Ranch Hand group versus the Comparison group over time.

SUMMARY

For the 1987 followup immunologic assessment, a number of unadjusted and adjusted analyses were performed using physical examination (composite skin test diagnosis) and laboratory examination data (cell surface marker studies, TLC, quantitative immunoglobulin measurements, and functional stimulation tests). The results of the Ranch Hand and Comparison group contrasts performed using the physical examination and laboratory examination data are summarized in Table 19-15.

For the composite skin test diagnosis, the unadjusted group contrast of the relative frequency of participants with possibly abnormal composite readings was significantly greater ($p=0.019$) for the Ranch Hands than the Comparisons. The adjusted model for the composite skin test results contained a significant group-by-lifetime cigarette smoking history interaction. Because of this interaction, the skin test results were analyzed for group differences through stratification of lifetime cigarette smoking history. Ranch Hands who smoked for over 10 pack-years had a significantly greater frequency of individuals with possibly abnormal skin test results than Comparisons with the same lifetime cigarette smoking history ($p=0.005$). Without the cited interaction, a significant adjusted group difference ($p=0.011$) remained.

For the cell surface marker studies of the 1987 followup, there were no significant group differences for either the unadjusted or the adjusted analyses. Except for CD25, the same cell surface marker variables were analyzed in both the 1985 and the 1987 followup studies. The 1985 followup unadjusted analyses for group differences were not significant. The 1985 followup adjusted analyses were not significant for CD4, CD8, and the CD4/CD8

TABLE 19-15.

Overall Summary Results of Unadjusted and Adjusted Analyses of Immunologic Variables

Variable	Type of Analysis	Unadjusted	Adjusted	Direction of Results
Physical Examination				
Composite Skin Test Diagnosis	D	0.019	** (0.011)	RH>C
Laboratory Examination: Quantitative Studies				
CD2 Cells	C	NS	NS	
CD4 Cells	C	NS	NS	
CD8 Cells	C	NS	NS	
CD20 Cells	C	NS	NS	
CD14 Cells	C	NS	NS	
CD25 Cells	D	NS	--	
	C	NS	NS	
HLA-DR Cells	C	NS	NS	
CD4/CD8 Ratio	C	NS	NS	
TLC	C	NS	NS	
IgG	C	NS	NS	
IgA	C	NS	NS	
IgM	C	NS	NS	
Laboratory Examination: Functional Stimulation Tests				
Unstimulated PHA Response	C	NS	NS	
PHA Net Response: Day 1				
Concentration 1	C	NS	** (NS)	
Concentration 2	C	NS	NS	
Concentration 3	C	NS	NS	
PHA Net Response: Day 2				
Concentration 1	C	NS	NS	
Concentration 2	C	NS	NS	
Concentration 3	C	NS	NS	
Overall PHA Net Response	C	NS	NS	
Maximum PHA Net Response	C	NS	NS	
Unstimulated MLC Response	C	NS	NS	
MLC Net Response	C	NS	** (NS)	
NKCA 50/1 Net Response	C	NS	** (NS)	
NKCA 50/1 Percent Release	C	NS	** (NS)	
NKCI 50/1 Net Response	C	NS	****	
NKCI 50/1 Percent Release	C	NS	****	

TABLE 19-15. (continued)

Overall Summary Results of Unadjusted and Adjusted Analyses of Immunologic Variables

D: Discrete analysis performed.

** (0.011): Group-by-covariate interaction ($0.01<p\leq0.05$); significant ($p=0.011$) when interaction is deleted.

RH>C: More abnormalities in Ranch Hands than in Comparisons.

C: Continuous analysis performed.

NS: Not significant ($p>0.10$).

--Analysis not done.

** (NS): Group-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Table P-3 for a detailed description of this interaction.

****: Group-by-covariate interaction ($p\leq0.01$); refer to Table P-3 for a detailed description of this interaction.

ratio; the remaining 1985 followup cell surface marker variables had significant group-by-covariate interactions in the adjusted models.

Unadjusted and adjusted group contrasts were not significant for TLC.

For each of the quantitative immunoglobulins (IgG, IgA, and IgM), the unadjusted and adjusted group contrasts were not significant.

For the functional stimulation tests of the 1987 followup study, unadjusted and adjusted analyses were performed on a number of measures pertaining to responses after mitogen stimulation with PHA, mixed lymphocyte responses to stimulation from donor lymphocytes, and NKCA and NKCI.

For the PHA responses, the group contrasts were performed for each of the following: unstimulated PHA responses for 2 harvest days concurrently; net responses to PHA at each of three concentrations on two different days; all PHA net responses concurrently for the six concentration and day combinations; and the maximum of the six PHA net responses.

For the 1987 followup, as in 1985, the unadjusted and adjusted group contrasts of the unstimulated PHA responses were not significant.

For the PHA net response for day 1, the unadjusted group contrast at each of the three concentration levels was not significant. The adjusted group contrasts of the PHA net response for day 1 at concentration levels 2 and 3 were also not significant. However, the adjusted analysis of the PHA net

response for day 1 at concentration level 1 had a significant group-by-current alcohol use interaction. For participants having over four drinks per day, Comparisons had a significantly greater net response to PHA for day 1 at concentration level 1 than Ranch Hands (p=0.024). For the PHA net response for day 2 at each of three concentration levels, the unadjusted and adjusted group contrasts were not significant. For the 1985 followup data, both the unadjusted and the adjusted group contrasts of the PHA net response did not exhibit significant group differences.

The unadjusted and adjusted simultaneous contrast of the six PHA net responses was not significant. The unadjusted and adjusted analyses of the maximum PHA net responses were not significant for the Ranch Hand versus Comparison group contrasts.

For the unstimulated MLC response, both the unadjusted and the adjusted group contrasts were not significant. For the MLC net response, the unadjusted group contrast was not significant and the adjusted analysis had a significant group-by-race interaction. Because of this interaction, group contrasts were performed within race strata. Among Blacks, the Ranch Hands had a marginally significantly lower average MLC net response than the Comparisons (p=0.059). An interaction with smoking history was seen in 1985.

For the NKCA and NKCI, 50/1 net responses and 50/1 percent releases were analyzed. In the Ranch Hand and Comparison group contrasts, the unadjusted analyses were not significant. For each of the adjusted analyses of the NKCA and NKCI variables, there was a significant group-by-race interaction. Because of these interactions, the NKCA 50/1 net responses and the 50/1 percent releases were analyzed within race strata. Black Ranch Hands had a borderline significantly greater average net response than Black Comparisons (p=0.065), and Black Ranch Hands had a significantly higher average percent release than their Comparisons (p=0.031). Deleting these interactions yielded nonsignificant group contrasts. For the NKCI assay, the group contrasts were also examined by race because of the significant group-by-race interaction. Black Ranch Hands had a significantly greater mean net response for NKCI than did the Black Comparisons (p=0.007). Black Ranch Hands had a significantly greater average percent release of NKCI than Black Comparisons (p=0.008), and nonblack Ranch Hands had a marginally significant lower average than nonblack Comparisons (p=0.069).

The unadjusted exposure index analysis of the composite skin test diagnosis was not significant for the enlisted flyers and for the enlisted groundcrew, and it was borderline significant (p=0.090) for the officers. For the adjusted exposure index analysis, officers had a significant exposure index-by-lifetime cigarette smoking history interaction and a significant exposure index-by-current alcohol use interaction. For enlisted flyers, there was a significant exposure index-by-lifetime alcohol history interaction. For enlisted groundcrew, there was a significant exposure index-by-lifetime alcohol history interaction and a significant exposure index-by-current alcohol use interaction.

For the exposure index analysis of the cell surface marker measures, the unadjusted analysis generally showed no significant difference for each occupation. For the adjusted exposure index analyses of an individual cell surface marker variable, an exposure index-by-covariate interaction was

generally found for at least one occupation. For the most part, the interactions involved the covariates of age, lifetime cigarette smoking history, current alcohol use, or lifetime alcohol history.

The unadjusted and adjusted exposure index analyses of TLC were not significant for officers and enlisted flyers. For the enlisted groundcrew, the unadjusted exposure index analysis was not significant, and the adjusted analysis contained a significant exposure index-by-lifetime cigarette smoking history interaction.

In general, the unadjusted exposure index analyses of the immunoglobulins were not significant for each occupation. For officers, the adjusted exposure index analysis of IgG was significant ($p=0.032$). For enlisted groundcrew, there was a significant exposure index-by-lifetime cigarette smoking history interaction for IgG. For officers and enlisted groundcrew, the adjusted exposure index analyses of IgA had significant exposure index-by-current cigarette smoking and exposure index-by-lifetime alcohol history interactions, respectively. The adjusted exposure index analyses of IgM were not significant.

For the exposure index analysis of the unstimulated PHA responses, the unadjusted and adjusted analyses for officers and for enlisted flyers were not significant. For enlisted groundcrew, the unadjusted exposure index analysis was not significant and the adjusted analysis contained significant interactions between the exposure index and both alcohol use covariates. For the PHA net responses for day 1 at each of three different concentration levels, the unadjusted and adjusted exposure index analyses were generally not significant for the three occupations. The exceptions occurred for enlisted flyers at concentration level 2 on the adjusted analysis ($p=0.053$), and for enlisted flyers at concentration level 3 on the unadjusted and the adjusted analyses ($p=0.067$ and $p=0.056$, respectively). For the PHA net responses for day 2 at each of three concentration levels, the unadjusted analyses were not significant for the three occupations. For the adjusted exposure index analyses of the PHA net responses for day 2, a significant exposure index-by-age interaction was found for the enlisted groundcrew at concentration level 1 and a significant exposure index-by-current cigarette smoking interaction was found for the officers at concentration level 3. For the simultaneous analysis of the six PHA net responses, neither the unadjusted nor the adjusted analysis was significant for each occupation. Similarly, neither the unadjusted nor the adjusted exposure index analysis of the maximum PHA net response was significant for each occupation.

The unadjusted exposure index analyses of the unstimulated MLC responses were not significant for each occupation. For the adjusted exposure index analysis of the unstimulated MLC responses, the enlisted flyers had a significant exposure index-by-age interaction, and the officers and the enlisted groundcrew displayed no significant difference for exposure index. For the MLC net responses, both the unadjusted and the adjusted exposure index analyses were not significant for each occupation.

The unadjusted exposure index analyses of the NKCA and NKCI net responses and percent releases were not significant for each occupation. For the exposure index adjusted analysis of the NKCA net response, the enlisted flyers had a significant exposure index-by-lifetime cigarette smoking history

interaction. For the exposure index adjusted analyses of the NKCA and the NKCI percent release, the enlisted groundcrew had significant exposure index-by-age interactions. Overall, the exploration of covariate interactions in the exposure index analyses detected scattered increases and decreases in cell count and functional assays that are impossible to interpret in the absence of a consensus as to what is abnormal for these measures of immunity.

The longitudinal analysis of the CD4/CD8 ratio results for the 1985 and 1987 followup examinations did not exhibit a significant group difference over time.

The immunologic assessment of laboratory data revealed no statistically significant differences between the Ranch Hands and Comparisons. The finding of a group difference in the proportion of participants possibly abnormal on the composite skin test diagnosis is of interest and will be reevaluated in the context of the quantitative serum dioxin levels. Overall, there appears to be no indication of clinically relevant impaired immunologic competence in the Ranch Hand group versus the Comparison group over time.

CHAPTER 19

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